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NOVEL COMPOUNDS

The present invention relates to a sulphonamide compound, processes and intermediates used in their preparation, pharmaceutical compositions containing them and their use in therapy.

Chemokines play an important role in immune and inflammatory responses in various diseases and disorders, including asthma and allergic diseases, as well as autoimmune pathologies such as rheumatoid arthritis and atherosclerosis. These small-secreted molecules are a growing superfamily of 8-14 kDa proteins characterised by a conserved four cysteine motif. At the present time, the chemokine superfamily comprises three groups exhibiting characteristic structural motifs, the Cys-X-Cys (C-X-C), Cys-Cys (C-C) and Cys-X_3-Cys (C-X_3-C) families. The C-X-C and C-C families have sequence similarity and are distinguished from one another on the basis of a single amino acid insertion between the NH-proximal pair of cysteine residues. The C-X_3-C family is distinguished from the other two families on the basis of having a triple amino acid insertion between the NH-proximal pair of cysteine residues.

The C-X-C chemokines include several potent chemoattractants and activators of neutrophils such as interleukin-8 (IL-8) and neutrophil-activating peptide 2 (NAP-2).

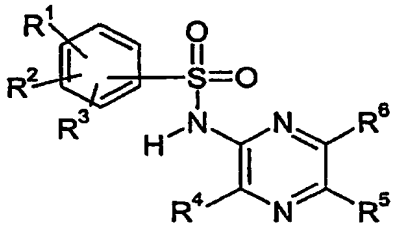
The C-C chemokines include potent chemoattractants of monocytes and lymphocytes but not neutrophils. Examples include human monocyte chemotactic proteins 1-3 (MCP-1, MCP-2 and MCP-3), RANTES (Regulated on Activation, Normal T Expressed and Secreted), eotaxin and the macrophage inflammatory proteins 1α and 1β (MIP-1α and MIP-1β), Thymus and Activation Regulated Chemokine (TARC, CCL17) and Macrophage Derived Chemokine (MDC, CCL22).

The C-X_3-C chemokine (also known as fractalkine) is a potent chemoattractant and activator of microglia in the central nervous system (CNS) as well as of monocytes, T cells, NK cells and mast cells.

Studies have demonstrated that the actions of chemokines are mediated by subfamilies of G protein-coupled receptors, among which are the receptors designated CCR1, CCR2, CCR2A, CCR2B, CCR3, CCR4, CCR5, CCR6, CCR7, CCR8, CCR9, CCR10 and CCR11

(for the C-C family); CXCR1, CXCR2, CXCR3, CXCR4 and CXCR5 (for the C-X-C family) and CX_3CR1 for the C-X_3-C family. These receptors represent good targets for drug development since agents which modulate these receptors would be useful in the treatment of disorders and diseases such as those mentioned above.

The present invention therefore provides a compound of formula (I) and pharmaceutically acceptable salts, solvates or N-oxides thereof:



(I)

in which

R^1, R^2 and R^3 are independently hydrogen, halogen, cyano, CF_3, OCF_3, C_{1-6} alkenyl or C_{1-6} alkyl;

R^4 is halogen, C_{1-6} alkoxy or OR^9;

R^5 and R^6 are independently hydrogen, halogen, C_{1-6} alkoxy, C_{1-6} alkylthio, cyano, R^9, OR^9, NR^9R^{10}, SR^9, $S(CH2)_nCO_2H$, $S(CH2)_nCO_2R^{12}$, $S(CH2)_nCONR^{12}R^{13}$, $S(CH2)_nR^{11}$ or a 5- to 7-membered heteroaromatic or saturated ring containing 1 to 3 heteroatoms selected from nitrogen, oxygen and sulphur;

n is 1, 2 or 3;

R^9 and R^{10} are independently hydrogen, C_{1-6} alkyl optionally substituted by hydroxy, C_{1-6} alkoxy or $NHCOC_{1-6}$ alkyl, or R^9 and R^{10} are optionally substituted aryl, C_{1-6} alkyl-aryl or C_{1-6} alkyl-R^{11} or R^9 and R^{10} together with the nitrogen atom to which they are attached form a 4- to 8-membered saturated ring containing 1 to 3 heteroatoms selected from nitrogen, oxygen and sulphur and optionally substituted by C_{1-6} alkyl or C_{1-6} alkyl-OH; and

R^{11} is a 5- to 7-membered heteraromatic ring containing 1 to 3 heteroatoms selected from nitrogen, oxygen and sulphur and optionally substituted by C_{1-6} alkyl; and

R^{12} and R^{13} are independently hydrogen or C_{1-6} alkyl.

The term aryl includes phenyl and naphthyl. Optional substituents for aryl groups include C_{1-6} alkyl, C_{1-6} alkoxy, halogen, CN, nitro, CO_2H, CO_2C_{1-6} alkyl etc. The term alkyl, whether alone or as part of another group, includes straight chain and branched chain alkyl

groups. Examples of 5- to 7-membered heteroaromatic ring containing 1 to 3 heteroatoms include thienyl, furanyl, imidazolyl, pyridyl, pyrazinyl and pyrimidyl. Examples of 4- to 8-membered heteraromatic ring containing 1 to 3 heteroatoms include morpholine, piperidine and azetidine. Substituents on any rings can be present in any suitable position including on nitrogen atoms.

Certain compounds of formula (I) are capable of existing in stereoisomeric forms. It will be understood that the invention encompasses all geometric and optical isomers of the compounds of formula (I) and mixtures thereof including racemates. Tautomers and mixtures thereof also form an aspect of the present invention.

R^1, R^2 and R^3 are independently hydrogen, halogen, cyano, CF_3, OCF_3, C_{1-6} alkenyl or C_{1-6} alkyl, preferred halogen groups being chloro. Preferably one of R^1, R^2 and R^3 is methyl, ethenyl, cyano, chloro, fluoro, iodo or two are chloro or all three are fluoro. More preferred are compounds where $R^1 - R^3$ together with the phenyl group to which they are attached form a 3-chloro-2-methylphenyl or a 2,3-dichlorophenyl group.

Preferred groups for R^4 include halogen such as bromo and chloro, C_{1-6} alkoxy such as methoxy and ethoxy, C_{1-6} alkyl or OR^9 where R^9 is CH_2R^{11} where R^{11} is a 5- or 6-membered heteraromatic ring containing 1 or 2 heteroatoms

More preferably R^4 is methoxy, halogen, such as chloro, or OR^9 where R^9 is CH_2R^{11} where R^{11} is furanyl, 5-methyl-3-isoxazolyl, pyridyl optionally substituted by methyl, pyridazinyl, pyrazinyl, 1-methyl-6-oxo-1,6-dihydro-3-pyridinyl.

Preferably R^5 is hydrogen, methyl, bromo, chloro, methoxy, morpholinyl, pyrrolinyl, dimethylamino, hydroxy, 2-methoxyethoxy, pyrazinyl, pyrimidinyl, O-Ph-CO_2H, 2-hydroxyethylamino, 2-methoxyethylamino, $NHCH_2CH_2NHCOMe$, cyano, 4-hydroxymethyl-1-piperidinyl, SMe, NHMe, or 2,4-difluorophenyl.

Preferably R^6 is hydrogen or chloro.

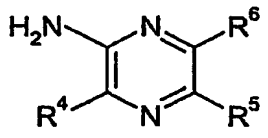
Preferred compounds of formula (I) include:
2,3-Dichloro-N-(3-methoxy-5-methyl-2-pyrazinyl)-benzenesulphonamide
N-(6-Chloro-3-methoxy-2-pyrazinyl)-2,3,4-tifluorobenzenesulphonamide
3-Chloro-N-(6-Chloro-3-methoxy-2-pyrazinyl)-2-methylbenzenesulphonamide

2,3-Dichloro-N-(6-Chloro-3-methoxy-2-pyrazinyl)benzenesulphonamide
2,3-Dichloro-N-(5-chloro-3-methoxy-2-pyrazinyl)benzenesulphonamide
N-(5-Bromo-3-methoxy-2-pyrazinyl)-2,5-dichlorobenzenesulphonamide
N-(5-Bromo-3-methoxy-2-pyrazinyl)-3,5-dichlorobenzenesulphonamide
N-(5-Bromo-3-methoxy-2-pyrazinyl)-2,3-dichlorobenzenesulphonamide
N-(5-Bromo-3-methoxy-2-pyrazinyl)-2,4-dichlorobenzenesulphonamide
N-(5-Bromo-3-methoxy-2-pyrazinyl)-3,4-dichlorobenzenesulphonamide
N-(5-Bromo-3-methoxy-2-pyrazinyl)-4-chlorobenzenesulphonamide
N-(5-Bromo-3-methoxy-2-pyrazinyl)-3-chlorobenzenesulphonamide
pyrazinamine
N-(5-Bromo-3-methoxy-2-pyrazinyl)-2-ethenylbenzenesulphonamide
N-(5-Bromo-3-methoxy-2-pyrazinyl)-2-fluorobenzenesulphonamide
N-(3-Methoxy-5-methyl-2-pyrazinyl)benzenesulphonamide
N-(3-Methoxy-5-methyl-2-pyrazinyl)-2-iodobenzenesulphonamide
N-(3-Methoxy-5-methyl-2-pyrazinyl)-3-fluorobenzenesulphonamide
2-[[(3-Methoxy-5-methyl-2-pyrazinyl)amino]sulphonyl]benzonitrile
N-(5-Bromo-3-methoxy-2-pyrazinyl)benzenesulphonamide
N-(5-Bromo-3-methoxy-2-pyrazinyl)2-iodobenzenesulphonamide
2,3-Dichloro-*N*-[3-(2-furanylmethoxy)-5-methyl-2-pyrazinyl)benzenesulphonamide
2,3-Dichloro-*N*-[5-methyl-3-(5-methyl-3-isoxazolylmethoxy)-2-pyrazinyl)benzenesulphonamide
2,3-Dichloro-*N*-[5-methyl-3-(2-pyridinylmethoxy)-2-pyrazinyl)benzenesulphonamide
2,3-Dichloro-*N*-[5-methyl-3-(6-methyl-2-pyridinylmethoxy)-2-pyrazinyl)benzenesulphonamide
2,3-Dichloro-*N*-[5-methyl-3-(3-pyridinylmethoxy)-2-pyrazinyl)benzenesulphonamide
2,3-Dichloro-*N*-[5-methyl-3-(4-pyridinylmethoxy)-2-pyrazinyl)benzenesulphonamide
2,3-Dichloro-*N*-[5-methyl-3-(3-methyl-2-pyridinylmethoxy)-2-pyrazinyl)benzenesulphonamide
2,3-Dichloro-*N*-[5-methyl-3-(3-pyridazinylmethoxy)-2-pyrazinyl)benzenesulphonamide
2,3-Dichloro-*N*-[3-(2-pyridinylmethoxy)-2-pyrazinyl)benzenesulphonamide
2,3-Dichloro-*N*-[3-(3-pyridinylmethoxy)-2-pyrazinyl)benzenesulphonamide
2,3-Dichloro-*N*-[3-methoxy-2-pyrazinyl)benzenesulphonamide
N-[5-Bromo-3-(2-pyrazinylmethoxy)-2-pyrazinyl]-2,3-dichlorobenzenesulphonamide
N-[5-Bromo-3-(1-methyl-6-oxo-1,6-dihydro-3-pyridinylmethoxy)-2-pyrazinyl]-2,3-dichlorobenzenesulphonamide
N-[5-Bromo-3-(3-pyridazinyllmethoxy)-2-pyrazinyl]-2,3-dichlorobenzenesulphonamide

N-[5-Bromo-3-(3-pyridinylmethoxy)-2-pyrazinyl]-2,3-dichlorobenzenesulphonamide
N-[5-Bromo-3-(5-pyrimidinylmethoxy)-2-pyrazinyl]-2,3-dichlorobenzenesulphonamide
N-[5-Chloro-3-(3-pyridinylmethoxy)-2-pyrazinyl]-2,3-dichlorobenzenesulphonamide
N-[5-Chloro-3-(5-pyrimidinylmethoxy)-2-pyrazinyl]-2,3-dichlorobenzenesulphonamide
2-Chloro-*N*-(6-chloro-3-methoxy-2-pyrazinyl)benezenesulphonamide
3-Chloro-*N*-(6-chloro-3-methoxy-2-pyrazinyl)benezenesulphonamide
4-Chloro-*N*-(6-chloro-3-methoxy-2-pyrazinyl)benezenesulphonamide
N-(6-Chloro-3-methoxy-2-pyrazinyl)-2,4-dichlorobenezenesulphonamide
3-Chloro-N-(3-methoxy-5-methyl-2-pyrazinyl)-2-methylbenezenesulphonamide
2-Chloro-*N*-(3-methoxy-5-methyl-2-pyrazinyl)benezenesulphonamide
3-Chloro-*N*-(3-methoxy-5-methyl-2-pyrazinyl)benezenesulphonamide
4-Chloro-*N*-(3-methoxy-5-methyl-2-pyrazinyl)benezenesulphonamide
2,4-Dichloro-*N*-(3-methoxy-5-methyl-2-pyrazinyl)benezenesulphonamide
3,4-Dichloro-*N*-(3-methoxy-5-methyl-2-pyrazinyl)benezenesulphonamide
N-(5-Bromo-3-methoxy-2-pyrazinyl)-2-trifluoromethoxybenezenesulphonamide
3-Chloro-*N*-(5-chloro-3-methoxy-2-pyrazinyl)-2-methylbenzenesulphonamide
2-Chloro-*N*-(5-chloro-3-methoxy-2-pyrazinyl)benzenesulphonamide
3-Chloro-*N*-(5-chloro-3-methoxy-2-pyrazinyl)benzenesulphonamide
4-Chloro-*N*-(5-chloro-3-methoxy-2-pyrazinyl)benzenesulphonamide
N-(5-Chloro-3-methoxy-2-pyrazinyl)-2,4-dichlorobenzenesulphonamide
2,3-Dichloro-*N*-[3-methoxy-5-(4-morpholinyl)-2-pyrazinyl]benzenesulphonamide
2,3-Dichloro-*N*-[3,5-dimethoxy-2-pyrazinyl]benzenesulphonamide
2,3-Dichloro-*N*-[3-methoxy-5-(1-pyrrolinyl)-2-pyrazinyl]benzenesulphonamide
3-Chloro-*N*-(5,6-dichloro-3-methoxy-2-pyrazinyl)-2-methylbenzenesulphonamide
2,3-Dichloro-*N*-(5,6-dichloro-3-methoxy-2-pyrazinyl)benzenesulphonamide
2-Chloro-*N*-(5,6-dichloro-3-methoxy-2-pyrazinyl)benzenesulphonamide
3-Chloro-*N*-(5,6-dichloro-3-methoxy-2-pyrazinyl)benzenesulphonamide
4-Chloro-*N*-(5,6-dichloro-3-methoxy-2-pyrazinyl)benzenesulphonamide
2,4-Dichloro-*N*-(5,6-dichloro-3-methoxy-2-pyrazinyl)benzenesulphonamide
3,4-Dichloro-*N*-(5,6-dichloro-3-methoxy-2-pyrazinyl)benzenesulphonamide
2,3-Dichloro-*N*-(3-methoxy-5,6-dimethyl-2-pyrazinyl)benzenesulphonamide
2,3-Dichloro-*N*-(6-chloro-3,5-dimethoxy-2-pyrazinyl)benzenesulphonamide
2,3-Dichloro-*N*-[6-chloro-3-methoxy-5-(4-morpholinyl)-2-pyrazinyl]benzenesulphonamide
2,3-Dichloro-*N*-[6-chloro-5-(2-hydroxyethylamino)-3-methoxy-2-pyrazinyl]benzenesulphonamide

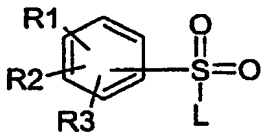
2,3-Dichloro-*N*-[6-chloro-5-dimethylamino-3-methoxy-2-pyrazinyl]benzenesulphonamide
2,3-Dichloro-*N*-[6-chloro-3-methoxy-5-(2-methoxyethoxy)-2-pyrazinyl]benzenesulphonamide
2,3-Dichloro-*N*-[6-chloro-5-hydroxy-3-methoxy-2-pyrazinyl]benzenesulphonamide
2,3-Dichloro-*N*-[6-methoxy-5-([2,2']bipyrazinylyl)]benzenesulphonamide
4-[5-(2,3-Dichlorobenzenesulphonylamino)-6-methoxy-pyrazin-2-yloxy]benzoic acid
2,3-Dichloro-*N*-(3,5-dichloro-2-pyrazinyl)benzenesulphonamide
2,3-Dichloro-*N*-[6-chloro-3-methoxy-5-({2-methoxyethyl}amino)-2-pyrazinyl]benzenesulphonamide
N-{2-[3-Chloro-5-(2,3-dichlorobenzenesulphonylamino)-6-methoxy-2-pyrazinylamino]ethyl}acetamide
2,3-Dichloro-*N*-[5-(4-hydroxymethyl-1-piperidinyl)-3-methoxy-2-pyrazinyl]benzenesulphonamide
2,3-Dichloro-*N*-[5-cyano-3-(3-pyridinylmethoxy)-2-pyrazinyl]benzenesulphonamide
2,3-Dichloro-*N*-(6-chloro-3-methoxy-5-methylamino-2-pyrazinyl)benzenesulphonamide
2,3-Dichloro-*N*-(3-methoxy-5-methylsulphanyl-2-pyrazinyl)benzenesulphonamide
2,3-Dichloro-*N*-[5-(2,4-difluorophenyl)-3-methoxy-2-pyrazinyl]benzenesulphonamide
[5-(2,3-Dichlorobenzenesulphonylamino)-6-methoxy-2-pyrazinylsulphanyl]acetic acid methyl ester
[5-(2,3-Dichlorobenzenesulphonylamino)-6-methoxy-2-pyrazinylsulphanyl]acetic acid
2,3-Dichloro-*N*-[5-(2-chlorobenzylsulphanyl)-3-methoxy-2-pyrazinyl]benzenesulphonamide
2,3-Dichloro-*N*-[6-chloro-5-(3-hydroxy-1-azetidinyl)-3-methoxy-2-pyrazinyl]benzenesulphonamide
2,3-Dichloro-*N*-[5-methyl-3-(1-oxy-3-pyrazinylmethoxy)-2-pyrazinyl]benzeesulphonamide
and pharmaceutically acceptable salts and solvates thereof.

According to the invention there is also provided a process for the preparation of compound (I) which comprises reaction of a compound of formula (II):



(II)

where R^4, R^5 and R^6 are as defined in formula (I) or are protected derivatives thereof with a compound of formula (III):



(III)

where R^1, R^2 and R^3 are as defined in formula (I) or are protected derivatives thereof and L is a leaving group,
and optionally thereafter
removing any protecting groups,
forming a pharmaceutically acceptable salt.

Preferred leaving groups L include chloro. Preferably the reaction between compounds (II) and (III) is carried out by treating compound (II) with a base such as sodium hydride in a suitable solvent such as DME.

It will be appreciated by those skilled in the art that in the processes of the present invention certain functional groups such as hydroxyl or amino groups in the starting reagents or intermediate compound may need to be protected by protecting groups. Thus, the preparation of the compound of formula (I) may involve, at an appropriate stage, the removal of one or more protecting groups. The protection and deprotection of functional groups is fully described in 'Protective Groups in Organic Chemistry', edited by J. W. F. McOmie, Plenum Press (1973), and 'Protective Groups in Organic Synthesis', 2nd edition, T. W. Greene & P. G. M. Wuts, Wiley–Interscience (1991).

Intermediate compounds of formula (II) and (III) can be prepared using standard chemistry or are available commercially.

Certain compounds of formula (I) are believed to be novel and form a further aspect of the invention.

The compounds of formula (I) above may be converted to a pharmaceutically acceptable salt or solvate thereof, preferably a basic addition salt such as sodium, potassium, calcium, aluminium, lithium, magnesium, zinc, benzathine, chloroprocaine, choline, diethanolamine, ethanolamine, ethyldiamine, meglumine, tromethamine or procaine, or an acid addition salt such as a hydrochloride, hydrobromide, phosphate, acetate, fumarate, maleate, tartrate, citrate, oxalate, methanesulphonate or *p*-toluenesulphonate.

The compounds of formula (I) have activity as pharmaceuticals, in particular as modulators of chemokine receptor (especially CCR4) activity, and may be used in the treatment (therapeutic or prophylactic) of conditions/diseases in human and non-human animals which are exacerbated or caused by excessive or unregulated production of chemokines. Examples of such conditions/diseases include:

(1) **(the respiratory tract)** obstructive airways diseases including chronic obstructive pulmonary disease (COPD); asthma, such as bronchial, allergic, intrinsic, extrinsic and dust asthma, particularly chronic or inveterate asthma (e.g. late asthma and airways hyper-responsiveness); bronchitis; acute, allergic, atrophic rhinitis and chronic rhinitis including rhinitis caseosa, hypertrophic rhinitis, rhinitis purulenta, rhinitis sicca and rhinitis medicamentosa; membranous rhinitis including croupous, fibrinous and pseudomembranous rhinitis and scrofoulous rhinitis; seasonal rhinitis including rhinitis nervosa (hay fever) and vasomotor rhinitis; sarcoidosis, farmer's lung and related diseases, fibroid lung and idiopathic interstitial pneumonia;

(2) **(bone and joints)** rheumatoid arthritis, seronegative spondyloarthropathies (including ankylosing spondylitis, psoriatic arthritis and Reiter's disease), Behcet's disease, Sjogren's syndrome and systemic sclerosis;

(3) **(skin)** psoriasis, atopical dermatitis, contact dermatitis and other eczmatous dermitides, seborrhoetic dermatitis, Lichen planus, Pemphigus, bullous Pemphigus, Epidermolysis bullosa, urticaria, angiodermas, vasculitides, erythemas, cutaneous eosinophilias, uveitis, Alopecia areata and vernal conjunctivitis, lupus;

(4) **(gastrointestinal tract)** Coeliac disease, proctitis, eosinopilic gastro-enteritis, mastocytosis, Crohn's disease, ulcerative colitis, food-related allergies which have effects remote from the gut, e.g., migraine, rhinitis and eczema;

(5) **(central and peripheral nervous system)** Neurodegenerative diseases and dementia disorders, e.g. Alzheimer's disease, amyotrophic lateral sclerosis and other motor neuron diseases, Creutzfeldt-Jacob's disease and other prion diseases, HIV encephalopathy (AIDS dementia complex), Huntington's disease, frontotemporal dementia, Lewy body dementia and vascular dementia; polyneuropathies, e.g. Guillain-Barré syndrome, chronic inflammatory demyelinating polyradiculoneuropathy, multifocal motor neuropathy, plexopathies; CNS demyelination, e.g. multiple sclerosis, acute disseminated/haemorrhagic encephalomyelitis, and subacute sclerosing panencephalitis; neuromuscular disorders, e.g. myasthenia gravis and Lambert-Eaton syndrome; spinal diorders, e.g. tropical spastic paraparesis, and stiff-man syndrome: paraneoplastic syndromes, e.g. cerebellar degeneration and encephalomyelitis; CNS trauma; migraine; and stroke.

(6) **(other tissues and systemic disease)** atherosclerosis, Acquired Immunodeficiency Syndrome (AIDS), lupus erythematosus, systemic lupus, erythematosus, Hashimoto's thyroiditis, type I diabetes, nephrotic syndrome, eosinophilia fascitis, hyper IgE syndrome, lepromatous leprosy, and idiopathic thrombocytopenia pupura; post-operative adhesions, and sepsis.

(7) (allograft rejection) acute and chronic following, for example, transplantation of kidney, heart, liver, lung, bone marrow, skin and cornea; and chronic graft versus host disease;

(8) Cancers, especially non-small cell lung cancer (NSCLC), malignant melanoma, prostate cancer and squamous sarcoma, Hodgkins Lymphoma, Acute Lymphoblastic Leukemia, and tumour metastasis;

(9) All diseases that result from a general inbalance of the immune system and resulting in increased atopic inflammatory reactions.

(10) Cystic fibrosis, re-perfusion injury in the heart, brain, peripheral limbs and other organs.

(11) Burn wounds & chronic skin ulcers

(12) Reproductive Diseases (e.g. Disorders of ovulation, menstruation and implantation, Pre-term labour, Endometriosis)

Thus, the present invention provides a compound of formula (I), or a pharmaceutically-acceptable salt or solvate thereof, as hereinbefore defined for use in therapy.

Preferably the compound of the invention are used to treat diseases in which the chemokine receptor belongs to the CC chemokine receptor subfamily, more preferably the target chemokine receptor is the CCR4 receptor.

Particular conditions which can be treated with the compound of the invention are asthma, rhinitis and inflammatory skin disorders, diseases in which there are raised TARC, MDC or CCR4 levels. It is preferred that the compound of the invention is used to treat asthma and rhinitis, especially asthma.

In a further aspect, the present invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined in the manufacture of a medicament for use in therapy.

In a still further aspect, the present invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined in the manufacture of a medicament for the treatment of human diseases or conditions in which modulation of chemokine receptor activity, particularly CCR4 activity, is beneficial.

In the context of the present specification, the term "therapy" also includes "prophylaxis" unless there are specific indications to the contrary. The terms "therapeutic" and "therapeutically" should be construed accordingly.

The invention still further provides a method of treating a chemokine mediated disease wherein the chemokine binds to a chemokine (especially CCR4) receptor, which comprises administering to a patient a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined.

The invention also provides a method of treating a respiratory disease, such as athma and rhinitis, especially asthma, in a patient suffering from, or at risk of, said disease, which comprises administering to the patient a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined.

For the above-mentioned therapeutic uses the dosage administered will, of course, vary with the compound employed, the mode of administration, the treatment desired and the disorder indicated.

The compound of formula (I) and pharmaceutically acceptable salts and solvates thereof may be used on their own but will generally be administered in the form of a pharmaceutical composition in which the formula (I) compound/salt/solvate (active ingredient) is in association with a pharmaceutically acceptable adjuvant, diluent or carrier. Depending on the mode of administration, the pharmaceutical composition will preferably comprise from 0.05 to 99 %w (per cent by weight), more preferably from 0.05 to 80 %w, still more preferably from 0.10 to 70 %w, and even more preferably from 0.10 to 50 %w, of active ingredient, all percentages by weight being based on total composition.

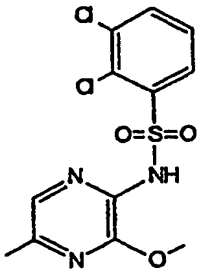
The present invention also provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined, in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

The invention further provides a process for the preparation of a pharmaceutical composition of the invention which comprises mixing a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined, with a pharmaceutically acceptable adjuvant, diluent or carrier.

The pharmaceutical compositions may be administered topically (e.g. to the lung and/or airways or to the skin) in the form of solutions, suspensions, heptafluoroalkane aerosols and dry powder formulations; or systemically, e.g. by oral administration in the form of tablets, capsules, syrups, powders or granules, or by parenteral administration in the form of solutions or suspensions, or by subcutaneous administration or by rectal administration in the form of suppositories or transdermally. Preferably the compound of the invention is administered orally.

Example 1

2,3-Dichloro-N-(3-methoxy-5-methyl-2-pyrazinyl)-benzenesulphonamide



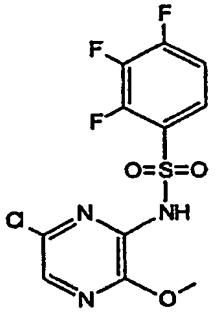
Sodium hydride (0.1g of 60%) was added to 3-methoxy-5-methyl-2-pyrazinamine (0.07g) in 1,2-dimethoxyethane (3mL) under nitrogen at room temperature. After 1 hour at 50°, 2,3-dichlorobenzenesuphonyl chloride (0.15g) was added. After stirring for 30 minutes, 5% aqueous citric acid was added and the product extracted with ethyl acetate (X3). The combined extracts were washed with saturated brine, dried ($MgSO_4$) and the solvent was evaporated. Chromatography on silica eluting with dichloromethane/methanol mixtures gave the title compound as a white solid (0.08g).

m/e 346/8/350 ($M-1^+$, 100%), HPLC 98.8%

^1H NMR (D6-DMSO) δ 11.27 (1H, s), 8.06 (1H, d), 7.93 (1H, d), 7.60-7.55 (1H, br s), 7.58 (1H, t), 3.87 (3H, s) and 2.28 (3H, s).

Example 2

N-(6-Chloro-3-methoxy-2-pyrazinyl)-2,3,4-tifluorobenzenesulphonamide



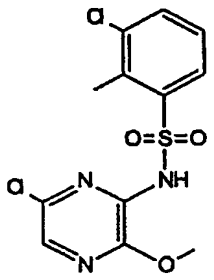
Prepared by the method of Example 1 using 6-chloro-3-methoxy-2-pyrazinamine and 2,3,4-trifluorobenzenesulphonyl chloride.

m/e 352/4 ($M-1^+$, 100%), HPLC 98.8%

^1H NMR (D6-DMSO) δ 7.93-7.80 (1H, m), 7.89 (1H, s), 7.60-7.50 (1H, m) and 3.91 (3H, s).

Example 3

3-Chloro-N-(6-Chloro-3-methoxy-2-pyrazinyl)-2-methylbenzenesulphonamide



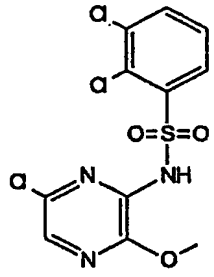
Prepared by the method of Example 1 using 6-chloro-3-methoxy-2-pyrazinamine and 3-chloro-2-methylbenzenesulphonyl chloride.

m/e 346/8/50 ($M-1^+$, 100%), HPLC 100%

^{1}H NMR (D6-DMSO) δ 8.05 (1H, d), 7.85 (1H, s), 7.75 (1H, d), 7.47 (1H, t), 3.92 (3H, s) and 2.66 (3H, s).

Example 4

2,3-Dichloro-N-(6-Chloro-3-methoxy-2-pyrazinyl)benzenesulphonamide



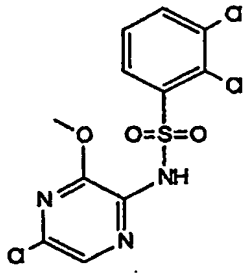
Prepared by the method of Example 1 using 6-chloro-3-methoxy-2-pyrazinamine and 2,3-dichlorobenzenesulphonyl chloride.

m/e 366/8/370/2 ($M-1^+$, 100%), HPLC 100%

^{1}H NMR (D6-DMSO) δ 8.14 (1H, d), 7.96 (1H, d), 7.89 (1H, s), 7.62 (1H, t) and 3.91 (3H, s).

Example 5

2,3-Dichloro-N-(5-chloro-3-methoxy-2-pyrazinyl)benzenesulphonamide



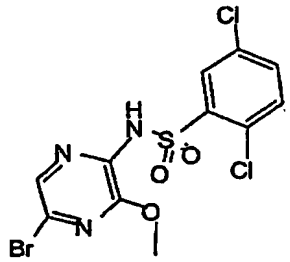
Prepared by the method of Example 1 using 5-chloro-3-methoxy-2-pyrazinamine and 2,3-dichlorobenzenesulphonyl chloride.

m/e 366/8/370/2 (M-1$^+$, 100%), HPLC 99.6%

^{1}H NMR (D6-DMSO) δ 8.15 (1H, d), 7.93 (1H, d), 7.79 (1H, s), 7.58 (1H, t) and 3.93 (3H, s).

Example 6

N-(5-Bromo-3-methoxy-2-pyrazinyl)-2,5-dichlorobenzenesulphonamide



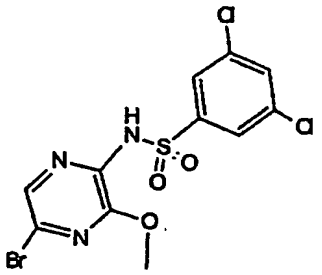
Prepared by the method of Example 1 using 5-bromo-3-methoxy-2-pyrazinamine and 2,5-dichlorobenzenesulphonyl chloride.

m/e 410/2/4/6 (M-1$^+$, 100%), HPLC 98.0%

^{1}H NMR (D6-DMSO) δ 8.04 (1H, d), 7.86 (1H, s), 7.73 (1H, dd), 7.66 (1H, dd) and 3.91 (3H, s).

Example 7

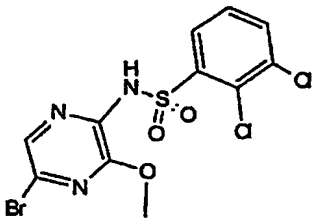
N-(5-Bromo-3-methoxy-2-pyrazinyl)-3,5-dichlorobenzenesulphonamide



Prepared by the method of Example 1 using 5-bromo-3-methoxy-2-pyrazinamine and 3,5-dichlorobenzenesulphonyl chloride.
m/e 410/2/4/6 ($M-1^+$, 100%), HPLC 96.1%
^{1}H NMR (D6-DMSO) δ 7.96-7.91 (4H, m) and 3.93 (3H, s).

Example 8

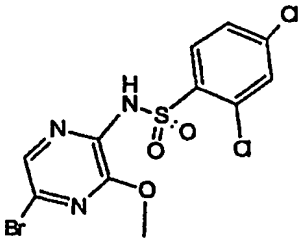
N-(5-Bromo-3-methoxy-2-pyrazinyl)-2,3-dichlorobenzenesulphonamide



Prepared by the method of Example 1 using 5-bromo-3-methoxy-2-pyrazinamine and 2,3-dichlorobenzenesulphonyl chloride.
m/e 410/2/4/6 ($M-1^+$, 100%), HPLC 97.3%
^{1}H NMR (D6-DMSO) δ 8.06 (1H, dd), 7.93 (1H, dd), 7.82 (1H, s), 7.57 (1H, t) and 3.92 (3H, s).

Example 9

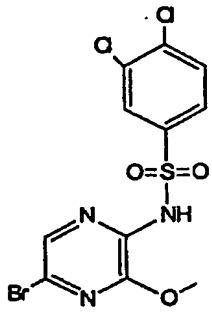
N-(5-Bromo-3-methoxy-2-pyrazinyl)-2,4-dichlorobenzenesulphonamide



Prepared by the method of Example 1 using 5-bromo-3-methoxy-2-pyrazinamine and 2,4-dichlorobenzenesulphonyl chloride.
m/e 410/2/4/6 ($M-1^+$, 100%), HPLC 99.9%
^{1}H NMR (D6-DMSO) δ 8.07 (1H, d), 7.85 (2H, d), 7.64 (1H, dd) and 3.92 (3H, s).

Example 10

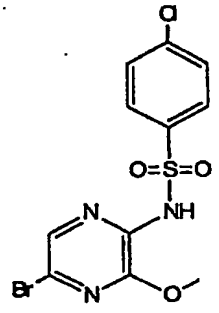
N-(5-Bromo-3-methoxy-2-pyrazinyl)-3,4-dichlorobenzenesulphonamide



Prepared by the method of Example 1 using 5-bromo-3-methoxy-2-pyrazinamine and 3,4-dichlorobenzenesulphonyl chloride.
m/e 410/2/4/6 ($M-1^+$, 100%), HPLC 98.8%
^{1}H NMR (D6-DMSO) δ 8.14 (1H, s), 8.00-7.85 (3H, m) and 3.94 (3H, s).

Example 11

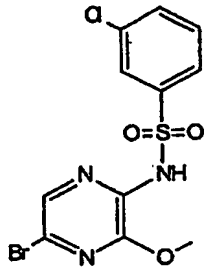
N-(5-Bromo-3-methoxy-2-pyrazinyl)-4-chlorobenzenesulphonamide



Prepared by the method of Example 1 using 5-bromo-3-methoxy-2-pyrazinamine and 4-chlorobenzenesulphonyl chloride.
m/e 376/8/380 ($M-1^+$, 100%), HPLC 98.8%
^{1}H NMR (D6-DMSO) δ 11.3 (1H, br s), 7.97 (2H, d), 7.91 (1H, s), 7.66 (2H, d) and 3.93 (3H, s).

Example 12

N-(5-Bromo-3-methoxy-2-pyrazinyl)-3-chlorobenzenesulphonamide



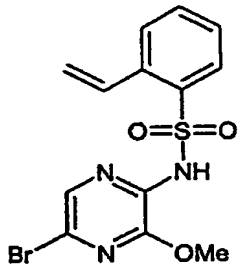
Prepared by the method of Example 1 using 5-bromo-3-methoxy-2-pyrazinamine and 3-chlorobenzenesulphonyl chloride.

m/e 376/8/380 ($M-1^+$, 100%), HPLC 97.8%

^{1}H NMR (D6-DMSO) δ 8.00-7.90 (3H, m), 7.75 (1H, d), 7.64 (1H, t) and 3.94 (3H, s).

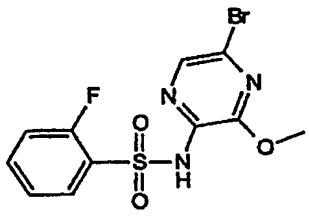
Example 13

N-(5-Bromo-3-methoxy-2-pyrazinyl)-2-ethenylbenzenesulphonamide



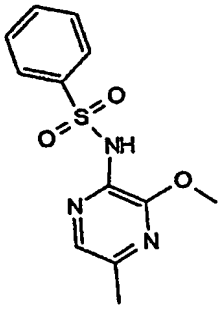
Example 14

N-(5-Bromo-3-methoxy-2-pyrazinyl)-2-fluorobenzenesulphonamide



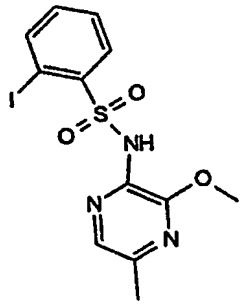
Example 15

N-(3-Methoxy-5-methyl-2-pyrazinyl)benzenesulphonamide



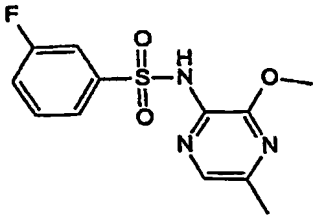
Example 16

N-(3-Methoxy-5-methyl-2-pyrazinyl)-2-iodobenzenesulphonamide



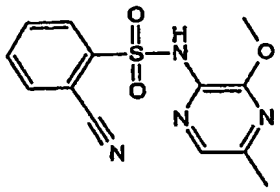
Example 17

N-(3-Methoxy-5-methyl-2-pyrazinyl)-3-fluorobenzenesulphonamide



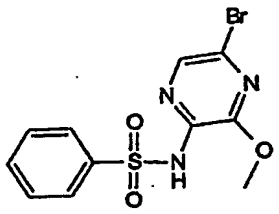
Example 18

2-[[(3-Methoxy-5-methyl-2-pyrazinyl)amino]sulphonyl]benzonitrile



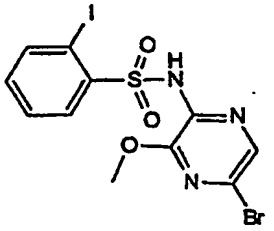
Example 19

N-(5-Bromo-3-methoxy-2-pyrazinyl)benzenesulphonamide



Example 19

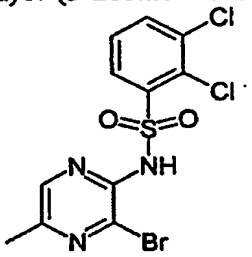
N-(5-Bromo-3-methoxy-2-pyrazinyl)2-iodobenzenesulphonamide



Example 20

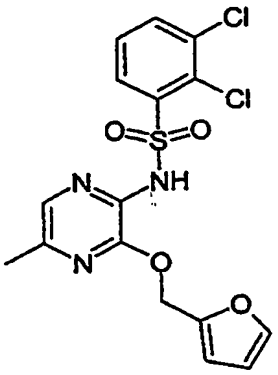
2,3-Dichloro-*N*-[3-(2-furanylmethoxy)-5-methyl-2-pyrazinyl)benzenesulphonamide

a) *N*-(3-Bromo-5-methyl-2-pyrazinyl)-2,3-dichlorobenzenesulphonamide



Prepared by the method of Example 1 using 3-bromo-5-methyl-2-pyrazinamine and 2,3-dichlorobenzenesulphonyl chloride.

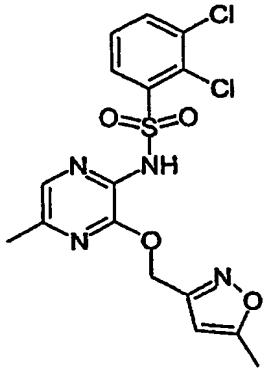
b) 2,3-Dichloro-*N*-[3-(2-furanylmethoxy)-5-methyl-2-pyrazinyl)benzenesulphonamide



Sodium hydride (0.04g of a 60% dispersion in oil) was added to furfurylalcohol (0.034g) in 1,2-dimethoxyethane (1mL). After 5 minutes *N*-(3-Bromo-5-methyl-2-pyrazinyl)-2,3-dichlorobenzenesulphonamide (Example 20 part a) (0.1g) was added and the mixture heated at 40 °C. After 16h, 5% aqueous citric acid (10mL) was added and the mixture extracted with ethyl acetate (2x50mL). The combined extracts were washed with brine, dried ($MgSO_4$) and the solvent evaporated. Chromatography on silica gel eluting with dichloromethane gave the title compound as a white solid (0.02g)
m/e 412 ($M\text{-}1^+$, 100%)
^{1}H NMR (D6-DMSO) δ 11.33 (1H, br s), 8.01 (1H, d), 7.90 (1H, d), 7.70 (1H, s), 7.62 (1H, br s), 7.54 (1H, t), 6.61-6.58 (1H, m), 6.50-6.45 (1H, m), 5.33 (2H, s), 2.32 (3H, s)
MP 127-129°C

Example 21

2,3-Dichloro-*N*-[5-methyl-3-(5-methyl-3-isoxazolylmethoxy)-2-pyrazinyl)benzenesulphonamide

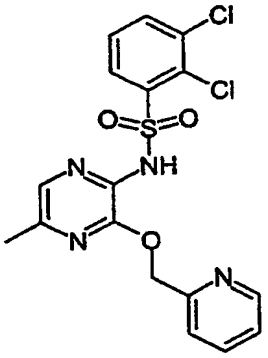


Prepared by the method of Example 20 using (5-methyl-3-isoxazolyl)methanol and *N*-(3-bromo-5-methyl-2-pyrazinyl)-2,3-dichlorobenzenesulphonamide.

m/e 429 ($M+1^+$, 100%)
^{1}H NMR (D6-DMSO) δ 11.39 (1H, br s), 8.03 (1H, d), 7.91 (1H, d), 7.64 (1H, br s), 7.47 (1H, t), 6.33 (1H, s), 5.37 (2H, s), 2.41 (3H, s), 2.29 (3H, s)
MP 155-156°C

Example 22

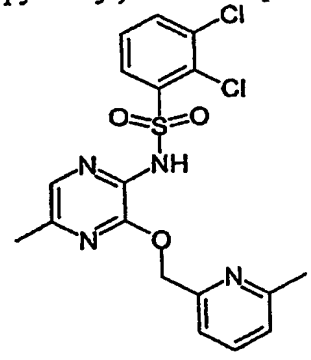
2,3-Dichloro-*N*-[5-methyl-3-(2-pyridinylmethoxy)-2-pyrazinyl)benzenesulphonamide



Prepared by the method of Example 20 using pyridine-2-methanol and *N*-(3-bromo-5-methyl-2-pyrazinyl)-2,3-dichlorobenzenesulphonamide.
m/e 425 ($M+1^+$, 100%)
^{1}H NMR (D6-DMSO) δ 8.57-8.54 (1H, m), 8.05 (1H, d), 7.89 (1H, d), 7.83 (1H, dt), 7.65-7.50 (2H, m), 7.56 (1H, t), 7.35-7.30 (1H, m), 5.44 (2H, s), 2.26 (3H, s)

Example 23

2,3-Dichloro-*N*-[5-methyl-3-(6-methyl-2-pyridinylmethoxy)-2-pyrazinyl)benzenesulphonamide

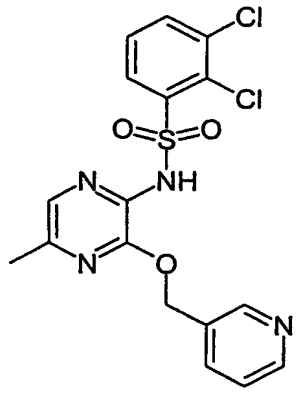


Prepared by the method of Example 20 using 6-methylpyridine-2-methanol and *N*-(3-bromo-5-methyl-2-pyrazinyl)-2,3-dichlorobenzenesulphonamide.

m/e 439 ($M+1^+$, 100%)
^{1}H NMR (D6-DMSO) δ 8.05 (1H, dd), 7.89 (1H, dd), 7.70 (1H, t), 7.59 (1H, br s), 7.54 (1H, t), 7.34 (1H, d), 7.19 (1H, d), 5.39 (2H, s), 2.47 (3H, s), 2.26 (3H, s)
MP 164-165°C

Example 24

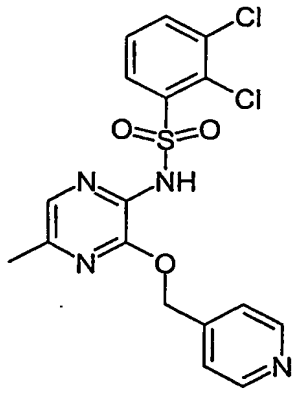
2,3-Dichloro-*N*-[5-methyl-3-(3-pyridinylmethoxy)-2-pyrazinyl)benzenesulphonamide



Prepared by the method of Example 20 using pyridine-3-methanol and *N*-(3-bromo-5-methyl-2-pyrazinyl)-2,3-dichlorobenzenesulphonamide.
m/e 425 ($M+1^+$, 100%)
^{1}H NMR (D6-DMSO) δ 8.74 (1H, d), 8.55 (1H, dd), 8.03 (1H, dd), 7.95-7.85 (2H, m), 7.59 (1H, br s), 7.54 (1H, t), 7.42 (1H, dd), 5.41 (2H, s), 2.29 (3H, s)
MP 160-161°C

Example 25

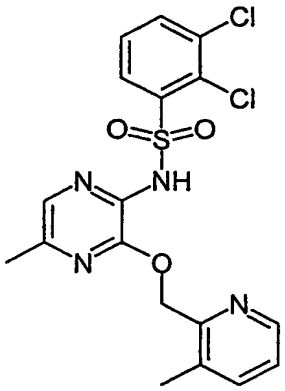
2,3-Dichloro-*N*-[5-methyl-3-(4-pyridinylmethoxy)-2-pyrazinyl)benzenesulphonamide



Prepared by the method of Example 20 using pyridine-4-methanol and *N*-(3-bromo-5-methyl-2-pyrazinyl)-2,3-dichlorobenzenesulphonamide.
m/e 425 ($M+1^+$, 100%)
^{1}H NMR (D6-DMSO) δ 8.57 (2H, d), 8.05 (1H, dd), 7.89 (1H, dd), 7.60 (1H, s), 7.55 (1H, t), 7.50 (2H, d), 5.43 (2H, s), 2.26 (3H, s)
MP 183-184°C

Example 26

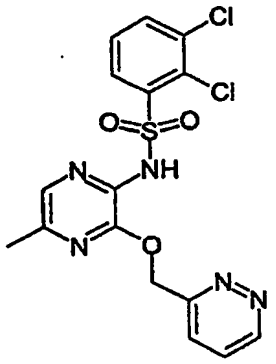
2,3-Dichloro-*N*-[5-methyl-3-(3-methyl-2-pyridinylmethoxy)-2-pyrazinyl)benzenesulphonamide



Prepared by the method of Example 20 using 3-methylpyridine-2-methanol and *N*-(3-bromo-5-methyl-2-pyrazinyl)-2,3-dichlorobenzenesulphonamide.
m/e 439 ($M+1^+$, 100%)
^{1}H NMR (D6-DMSO) δ 8.36 (1H, d), 8.05 (1H, dd), 7.83 (1H, dd), 7.64 (1H, d), 7.60 (1H, br s), 7.49 (1H, t), 7.31 (1H, dd), 5.40 (2H, s), 2.33 (3H, s), 2.29 (3H, s)
MP 137-138°C

Example 27

2,3-Dichloro-*N*-[5-methyl-3-(3-pyridazinylmethoxy)-2-pyrazinyl)benzenesulphonamide

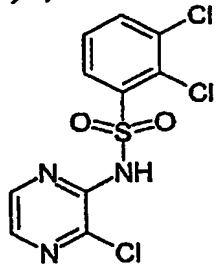


Prepared by the method of Example 20 using pyridazine-3-methanol and *N*-(3-bromo-5-methyl-2-pyrazinyl)-2,3-dichlorobenzenesulphonamide.
m/e 424 ($M-1^+$, 100%)
^{1}H NMR (D6-DMSO) δ 11.47 (1H, br s), 9.21 (1H, dd), 8.05 (1H, dd), 8.00-7.95 (1H, m), 7.88 (1H, d), 7.80-7.75 (1H, m), 7.62 (1H, br s), 7.54 (1H, t), 5.65 (2H, s), 2.27 (3H, s)
MP 119-124°C

Example 28

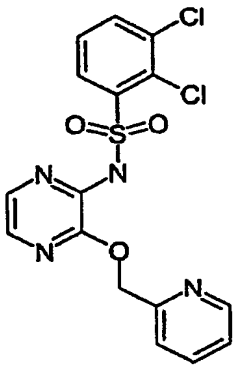
2,3-Dichloro-*N*-[3-(2-pyridinylmethoxy)-2-pyrazinyl)benzenesulphonamide

a) 2,3-Dichloro-*N*-(3-chloro-2-pyrazinyl)benzenesulphonamide



2,3-Dichloropyrazine (2.6g), 2,3-dichlorobenzenesulphonamide (4.0g) and potassium carbonate (10.0g) in *N,N*-dimethylformamide (50mL) was heated at 75°C.
After 16h, 5% aqueous citric acid (30mL) was added and the mixture extracted with ethyl acetate (2x100mL). The combined extracts were washed with brine, dried ($MgSO_4$) and the solvent evaporated. Chromatography on silica gel eluting with ethyl acetate/isohexane mixtures gave the title compound (1.5g).

b) 2,3-Dichloro-*N*-[3-(2-pyridinylmethoxy)-2-pyrazinyl)benzenesulphonamide



Sodium hydride (0.05g of a 60% dispersion in oil) was added to pyridine-2-methanol (0.088g) in 1,2-dimethoxyethane (3.0mL). After 5 minutes, 2,3-Dichloro-*N*-(3-chloro-2-pyrazinyl)benzenesulphonamide (0.1g) was added and the mixture heated at 70°C. After 4h, 5% aqueous citric acid (10mL) was added and the mixture extracted with ethyl acetate (2x50mL). The combined extracts were washed with brine, dried ($MgSO_4$) and the solvent evaporated. Chromatography on silica gel eluting with ethyl acetate/isohexane mixtures gave the title compound as a white solid (0.06g).

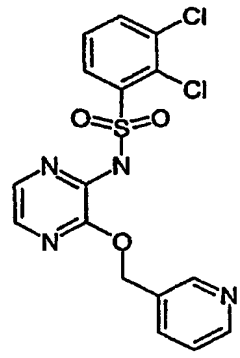
m/e 411 ($M+1^+$, 100%)

^1H NMR (D6-DMSO) δ 8.57 (1H, d), 8.13 (1H, d), 7.93 (1H, d), 7.90-7.75 (2H, m), 7.75-7.65 (1H, m), 7.65-7.55 (2H, m), 7.40-7.30 (1H, m), 5.49 (2H, s)

MP 167-168°C

Example 29

2,3-Dichloro-*N*-[3-(3-pyridinylmethoxy)-2-pyrazinyl)benzenesulphonamide



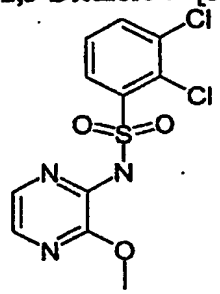
Prepared by the method of Example 28 using pyridine-3-methanol and 2,3-dichloro-*N*-(3-chloro-2-pyrazinyl)benzenesulphonamide.

m/e 409 ($M-1^+$, 100%)

^{1}H NMR ($CDCl_3$) δ 8.70 (1H, s), 8.65 (1H, d), 8.28 (1H, dd), 7.79 (1H, d), 7.70-7.67 (2H, m), 7.61 (1H, d), 7.40-7.35 (2H, m), 5.45 (2H, s)
MP 138-139°C

Example 30

2,3-Dichloro-*N*-[3-methoxy-2-pyrazinyl)benzenesulphonamide

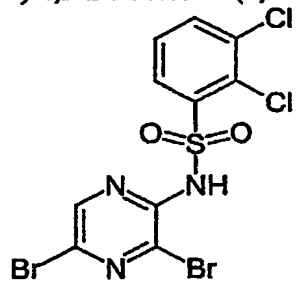


2,3-Dichloro-*N*-(3-chloro-2-pyrazinyl)benzenesulphonamide (Example 28 part a) (0.2g) in 10% sodium methoxide in methanol (10mL) was heated at 85°C. After 4h, 5% aqueous citric acid (50mL) was added and the mixture extracted with ethyl acetate (2x150mL). The combined extracts were washed with brine, dried ($MgSO_4$) and the solvent evaporated. Chromatography on silica gel eluting with ethyl acetate/isohexane mixtures gave the title compound as a white solid (0.12g)
m/e 334 ($M+1^+$, 100%)
^{1}H NMR (D6-DMSO) δ 11.54 (1H, br s), 8.10 (1H, d), 7.94 (1H, d), 7.85-7.75 (1H, m), 7.70-7.55 (1H, m), 7.59 (1H, t), 3.90 (3H, s)
MP 183-184°C

Example 31

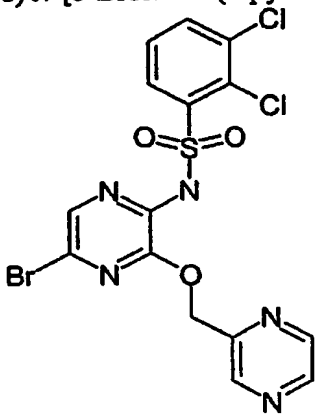
N-[5-Bromo-3-(2-pyrazinylmethoxy)-2-pyrazinyl]-2,3-dichlorobenzenesulphonamide

a) 2,3-Dichloro-*N*-(3,5-dibromo-2-pyrazinyl)benzenesulphonamide



Prepared by the method of Example 1 using 3,5-dibromo-2-pyrazinamine and 2,3-dichloro benzenesulphonyl chloride.

b) *N*-[5-Bromo-3-(2-pyrazinylmethoxy)-2-pyrazinyl]-2,3-dichlorobenzenesulphonamide



Sodium hydride (0.05g of a 60% dispersion in oil) was added to pyrazine-2-methanol (0.04g) in 1,2-dimethoxyethane (3ml). After 5 minutes, 2,3-Dichloro-*N*-(3,5-dibromo-2-pyrazinyl)benzenesulphonamide (0.12g) was added. After 0.5h, 5% aqueous citric acid (10mL) was added and the mixture extracted with ethyl acetate (2x30mL). The combined extracts were washed with brine, dried ($MgSO_4$) and the solvent evaporated. Chromatography on silica gel eluting with ethyl acetate/isohexane mixtures gave the title compound as a white solid (0.06g).

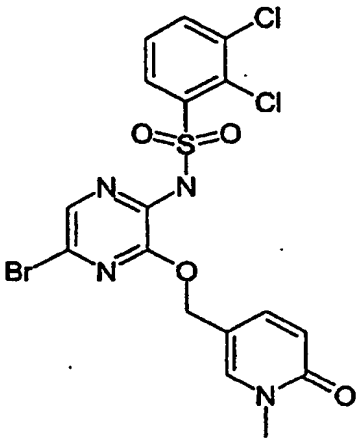
m/e 489 ($M\text{-}1^+$, 100%)

^{1}H NMR (D6-DMSO) δ 9.00 (1H, s), 8.66 (2H, s), 8.08 (1H, dd), 7.92 (1H, dd), 7.91 (1H, s), 7.56 (1H, t), 5.53 (2H, s)

MP 207-209°C

Example 32

N-[5-Bromo-3-(1-methyl-6-oxo-1,6-dihydro-3-pyridinylmethoxy)-2-pyrazinyl]-2,3-dichlorobenzenesulphonamide



Prepared by the method of Example 31 using 5-hydroxymethyl-1-methyl-1H-pyridin-2-one and 2,3-dichloro-*N*-(3,5-dibromo-2-pyrazinyl)benzenesulphonamide.

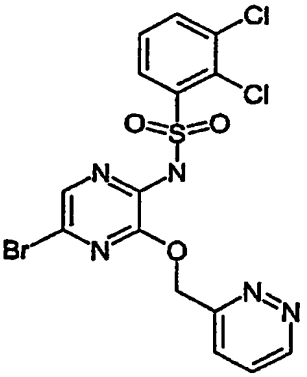
m/e 521 ($M+1^+$, 100%)

^{1}H NMR (D6-DMSO) δ 8.04 (1H, dd), 7.91 (1H, dd), 7.90-7.87 (2H, m), 7.60-7.50 (2H, m), 6.42 (1H, d), 5.10 (2H, s), 3.41 (3H, s)

MP 169-170°C

Example 33

N-[5-Bromo-3-(3-pyridazinyllmethoxy)-2-pyrazinyl]-2,3-dichlorobenzenesulphonamide



Prepared by the method of Example 31 using pyridazine-3-methanol and 2,3-dichloro-*N*-(3,5-dibromo-2-pyrazinyl)benzenesulphonamide.

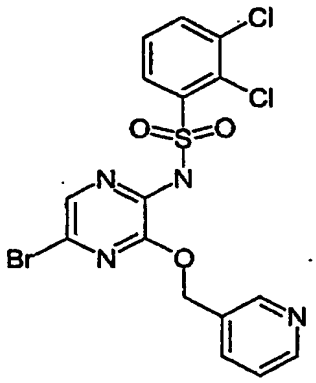
m/e 489 ($M-1^+$, 100%)

^{1}H NMR (D6-DMSO) δ 9.23 (1H, d), 8.08 (1H, dd), 7.99 (1H, dd), 7.92 (1H, dd), 7.91 (1H, s), 7.80 (1H, dd), 7.56 (1H, t), 5.67 (2H, s)

MP 115-120°C

Example 34

N-[5-Bromo-3-(3-pyridinylmethoxy)-2-pyrazinyl]-2,3-dichlorobenzenesulphonamide



Prepared by the method of Example 31 using pyridine-3-methanol and 2,3-dichloro-*N*-(3,5-dibromo-2-pyrazinyl)benzenesulphonamide.

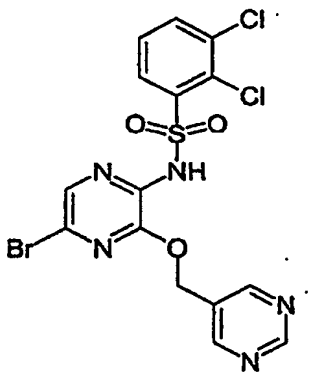
m/e 491 ($M+1^+$, 100%)

^{1}H NMR (D6-DMSO) δ 8.78 (1H, d), 8.58 (1H, dd), 8.06 (1H, d), 7.99 (1H, dt), 7.91 (1H, d), 7.88 (1H, s), 7.55 (1H, t), 7.55-7.50 (1H, m), 5.44 (2H, s)

MP 204-206°C

Example 35

N-[5-Bromo-3-(5-pyrimidinylmethoxy)-2-pyrazinyl]-2,3-dichlorobenzenesulphonamide



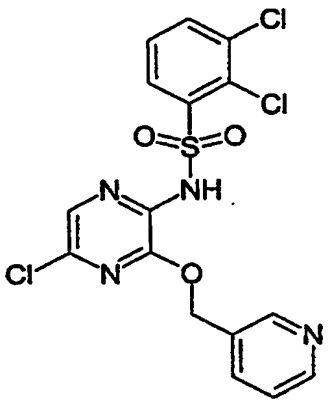
Prepared by the method of Example 31 using pyrimidine-5-methanol and 2,3-dichloro-*N*-(3,5-dibromo-2-pyrazinyl)benzenesulphonamide.

m/e 490 ($M-1^+$, 100%)

^{1}H NMR (D6-DMSO) δ 9.21 (1H, s), 9.02 (2H, s), 8.07 (1H, dd), 7.92 (1H, dd), 7.91 (1H, s), 7.56 (1H, t), 5.45 (2H, s)
MP 208-209°C

Example 36

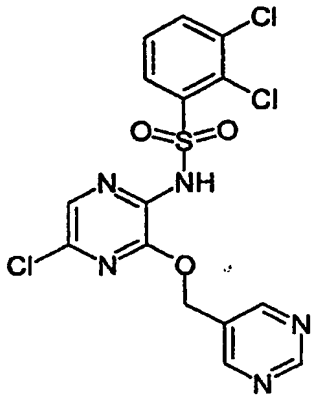
N-[5-Chloro-3-(3-pyridinylmethoxy)-2-pyrazinyl]-2,3-dichlorobenzenesulphonamide



Prepared by the method of Example 31 using pyridine-3-methanol and 2,3-dichloro-*N*-(3,5-dichloro-2-pyrazinyl)benzenesulphonamide (Example 74).
m/e 447 ($M+1^+$, 100%)
^{1}H NMR (D6-DMSO) δ 8.78 (1H, s), 8.59 (1H, dd), 8.06 (1H, dd), 7.96 (1H, dt), 7.91 (1H, dd), 7.83 (1H, s), 7.55 (1H, t), 7.47 (1H, dd), 5.44 (2H, s)
MP 200-204°C

Example 37

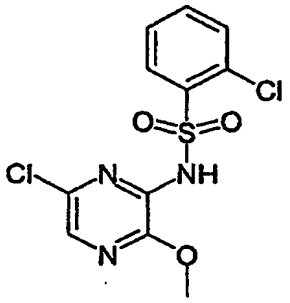
N-[5-Chloro-3-(5-pyrimidinylmethoxy)-2-pyrazinyl]-2,3-dichlorobenzenesulphonamide



Prepared by the method of Example 31 using pyrimidine-5-methanol and 2,3-dichloro-*N*-(3,5-dichloro-2-pyrazinyl)benzenesulphonamide (Example 74).
m/e 448 ($M+1^+$, 100%)
^{1}H NMR (D6-DMSO) δ 9.21 (1H, s), 9.02 (2H, s), 8.08 (1H, dd), 7.92 (1H, dd), 7.86 (1H, s), 7.56 (1H, t), 5.46 (2H, s)
MP 205-206°C

Example 38

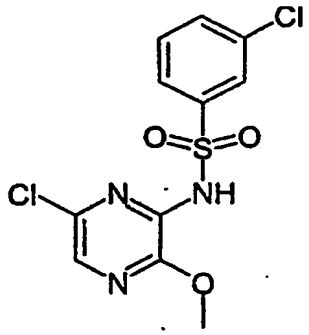
2-Chloro-*N*-(6-chloro-3-methoxy-2-pyrazinyl)benezenesulphonamide



Prepared by the method of Example 1 using 6-chloro-3-methoxy-2-pyrazinamine and 2-chlorobenzenesulphonyl chloride.
m/e 332 ($M-1^+$, 100%)
^{1}H NMR (D6-DMSO) δ 8.15 (1H, d), 7.86 (1H, s), 7.70-7.50 (3H, m), 3.91 (3H, s)
MP 172-173°C

Example 39

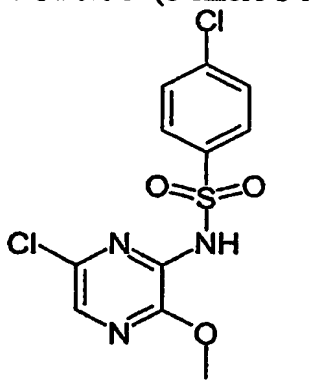
3-Chloro-*N*-(6-chloro-3-methoxy-2-pyrazinyl)benezenesulphonamide



Prepared by the method of Example 1 using 6-chloro-3-methoxy-2-pyrazinamine and 3-chlorobenzenesulphonyl chloride.
m/e 332 ($M-1^+$, 100%)
^{1}H NMR (D6-DMSO) δ 8.05 (1H, d), 7.93 (1H, dd), 7.90 (1H, s), 7.76 (1H, dd), 7.65 (1H, t) 3.92 (3H, s)
MP 126-127°C

Example 40

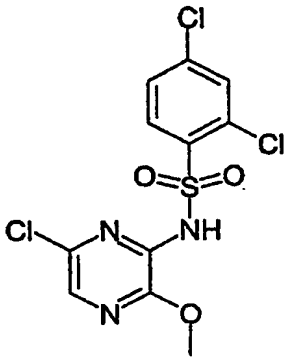
4-Chloro-*N*-(6-chloro-3-methoxy-2-pyrazinyl)benezenesulphonamide



Prepared by the method of Example 1 using 6-chloro-3-methoxy-2-pyrazinamine and 4-chlorobenzenesulphonyl chloride.
m/e 332 ($M-1^+$, 100%)
^{1}H NMR (D6-DMSO) δ 7.99 (2H, dt), 7.89 (1H, s), 7.70 (2H, dt), 3.92 (3H, s)
MP 174-175°C

Example 41

N-(6-Chloro-3-methoxy-2-pyrazinyl)-2,4-dichlorobenezenesulphonamide



Prepared by the method of Example 1 using 6-chloro-3-methoxy-2-pyrazinamine and 2,4-dichlorobenzenesulphonyl chloride.

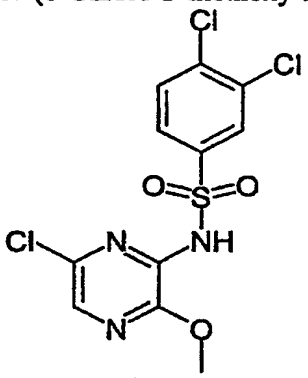
m/e 368 ($M-1^+$, 100%)

^{1}H NMR (D6-DMSO) δ 8.13 (1H, d), 7.86 (1H, s), 7.85 (1H, d), 7.70 (1H, dd), 3.91 (3H, s)

MP 189-190°C

Example 42

N-(6-Chloro-3-methoxy-2-pyrazinyl)-3,4-dichlorobenezenesulphonamide



Prepared by the method of Example 1 using 6-chloro-3-methoxy-2-pyrazinamine and 3,4-dichlorobenzenesulphonyl chloride.

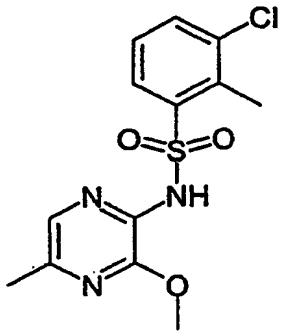
m/e 368 ($M-1^+$, 100%)

^{1}H NMR (D6-DMSO) δ 8.21 (1H, s), 7.93-7.90 (3H, m), 3.92 (3H, s)

MP 176-177°C

Example 43

3-Chloro-N-(3-methoxy-5-methyl-2-pyrazinyl)-2-methylbenezenesulphonamide



Prepared by the method of Example 1 using 3-methoxy-5-methyl-2-pyrazinamine and 3-chloro-2-methylbenzenesulphonyl chloride.

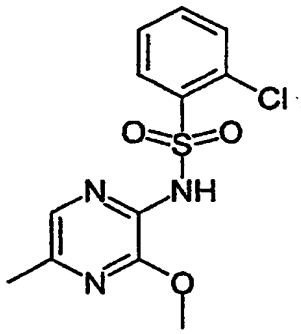
m/e 328 ($M+1^+$, 100%)

^{1}H NMR (D6-DMSO) δ 11.09 (1H, br s), 7.95 (1H, d), 7.72 (1H, d), 7.54 (1H, br s), 7.41 (1H, t), 3.88 (3H, s), 2.64 (3H, s), 2.27 (3H, s)

MP 133-135°C

Example 44

2-Chloro-*N*-(3-methoxy-5-methyl-2-pyrazinyl)benezenesulphonamide



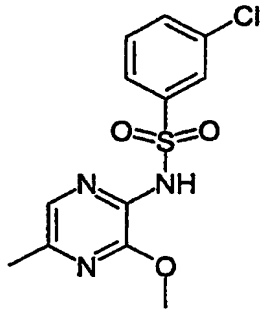
Prepared by the method of Example 1 using 3-methoxy-5-methyl-2-pyrazinamine and 2-chlorobenzenesulphonyl chloride.

m/e 314 ($M+1^+$, 100%)

^{1}H NMR (D6-DMSO) δ 11.07 (1H, br s), 8.06 (1H, d), 7.69-7.46 (4H, m), 3.90 (3H, s), 2.24 (3H, s)

Example 45

3-Chloro-*N*-(3-methoxy-5-methyl-2-pyrazinyl)benezenesulphonamide



Prepared by the method of Example 1 using 3-methoxy-5-methyl-2-pyrazinamine and 3-chlorobenzenesulphonyl chloride.

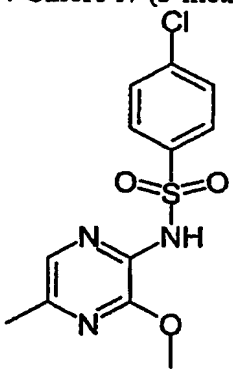
m/e 314 ($M+1^+$, 100%)

^{1}H NMR (D6-DMSO) δ 10.89 (1H, br s), 7.97 (1H, d), 7.92 (1H, d), 7.73 (1H, d), 7.65-7.58 (2H, m), 3.90 (3H, s), 2.29 (3H, s)

MP 123-125°C

Example 46

4-Chloro-*N*-(3-methoxy-5-methyl-2-pyrazinyl)benezenesulphonamide



Prepared by the method of Example 1 using 3-methoxy-5-methyl-2-pyrazinamine and 4-chlorobenzenesulphonyl chloride.

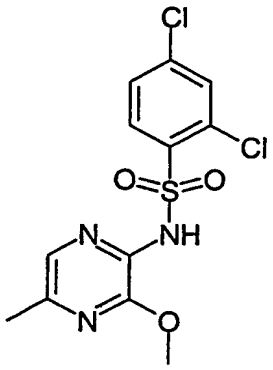
m/e 314 ($M+1^+$, 100%)

^{1}H NMR (D6-DMSO) δ 10.83 (1H, br s), 7.96 (2H, d), 7.65 (2H, d), 7.60 (1H, s), 3.88 (3H, s), 2.28 (3H, s)

MP 155-156°C

Example 47

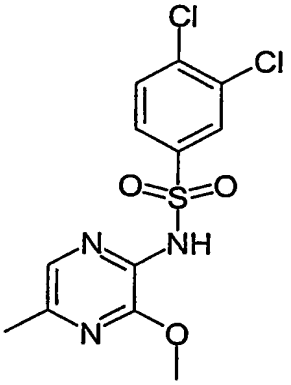
2,4-Dichloro-*N*-(3-methoxy-5-methyl-2-pyrazinyl)benezenesulphonamide



Prepared by the method of Example 1 using 3-methoxy-5-methyl-2-pyrazinamine and 2,4-dichlorobenzenesulphonyl chloride.
m/e 348 ($M+1^+$, 100%)
^{1}H NMR (D6-DMSO) δ 8.05 (1H, d), 7.83 (1H, d), 7.64 (1H, dd), 7.54 (1H, br s), 3.87 (3H, s), 2.27 (3H, s)
MP 135-136°C

Example 48

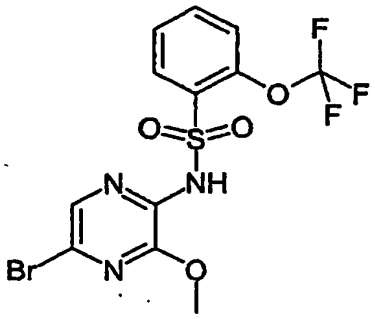
3,4-Dichloro-*N*-(3-methoxy-5-methyl-2-pyrazinyl)benezenesulphonamide



Prepared by the method of Example 1 using 3-methoxy-5-methyl-2-pyrazinamine and 3,4-dichlorobenzenesulphonyl chloride.
m/e 348 ($M+1^+$, 100%)
^{1}H NMR (D6-DMSO) δ 10.97 (1H, s), 8.14 (1H, d), 7.91 (1H, dd), 7.88 (1H, d), 7.63 (1H, s), 3.89 (3H, s), 2.27 (3H, s)
MP 148-149°C

Example 49

N-(5-Bromo-3-methoxy-2-pyrazinyl)-2-trifluoromethoxybenezenesulphonamide



Prepared by the method of Example 1 using 5-bromo-3-methoxy-2-pyrazinamine and 2-trifluoromethoxybenzenesulphonyl chloride.

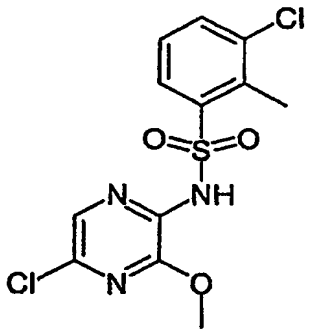
m/e 428 ($M-1^+$, 100%)

^{1}H NMR (D6-DMSO) δ 8.03 (1H, dd), 7.87 (1H, s), 7.82-7.74 (1H, m), 7.60-7.52 (2H, m), 3.92 (3H, s)

MP 156-157°C

Example 50

3-Chloro-*N*-(5-chloro-3-methoxy-2-pyrazinyl)-2-methylbenzenesulphonamide



Prepared by the method of Example 1 using 5-chloro-3-methoxy-2-pyrazinamine and 3-chloro-2-methylbenzenesulphonyl chloride.

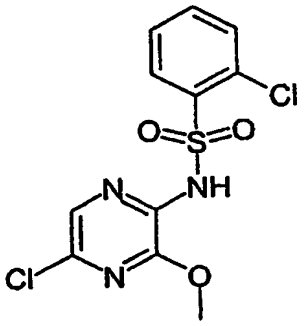
m/e 346 ($M-1^+$, 100%)

^{1}H NMR ($CDCl_3$) δ 8.17 (1H, d), 7.69 (1H, br s), 7.64 (1H, s), 7.61 (2H, d), 7.30 (1H, t), 4.04 (3H, s), 2.73 (3H, s)

MP 150-152°C

Example 51

2-Chloro-*N*-(5-chloro-3-methoxy-2-pyrazinyl)benzenesulphonamide



Prepared by the method of Example 1 using 5-chloro-3-methoxy-2-pyrazinamine and 2-chlorobenzenesulphonyl chloride.

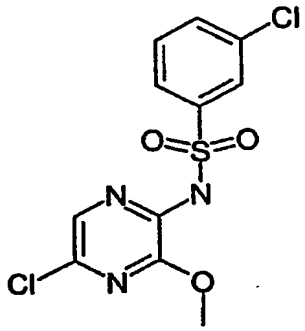
m/e 332 ($M+1^+$, 100%)

^{1}H NMR ($CDCl_3$) δ 8.33 (1H, d), 7.82 (1H, s), 7.64-7.62 (1H, m), 7.61 (1H, s), 7.50-7.42 (2H, m), 4.04 (3H, s)

MP 190-192°C

Example 52

3-Chloro-*N*-(5-chloro-3-methoxy-2-pyrazinyl)benzenesulphonamide



Prepared by the method of Example 1 using 5-chloro-3-methoxy-2-pyrazinamine and 3-chlorobenzenesulphonyl chloride.

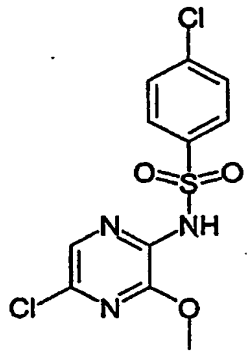
m/e 332 ($M+1^+$, 100%)

^{1}H NMR ($CDCl_3$) δ 8.14 (1H, s), 8.03 (1H, d), 7.76 (1H, s), 7.68-7.53 (2H, m), 7.46 (1H, t), 4.02 (3H, s)

MP 129-130°C

Example 53

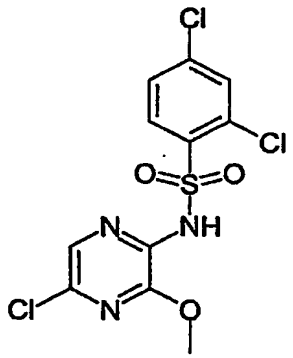
4-Chloro-*N*-(5-chloro-3-methoxy-2-pyrazinyl)benzenesulphonamide



Prepared by the method of Example 1 using 5-chloro-3-methoxy-2-pyrazinamine and 4-chlorobenzenesulphonyl chloride.
m/e 332 ($M+1^+$, 100%)
^{1}H NMR ($CDCl_3$) δ 8.07 (2H, d), 7.75 (1H, s), 7.56 (1H, s), 7.49 (2H, d), 4.02 (3H, s)
MP 179-180°C

Example 54

N-(5-Chloro-3-methoxy-2-pyrazinyl)-2,4-dichlorobenzenesulphonamide

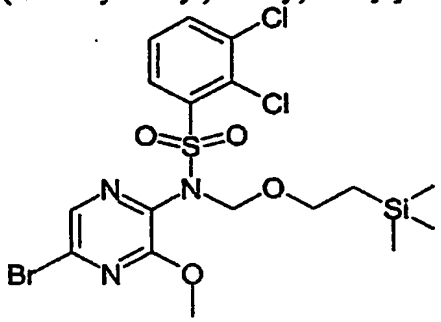


Prepared by the method of Example 1 using 5-chloro-3-methoxy-2-pyrazinamine and 2,4-dichlorobenzenesulphonyl chloride.
m/e 368 ($M-1^+$, 100%)
^{1}H NMR ($CDCl_3$) δ 8.27 (1H, d), 7.78 (1H, s), 7.63 (1H, s), 7.48 (1H, s), 7.43 (1H, d), 4.05 (3H, s)
MP 170-171°C

Example 55

2,3-Dichloro-*N*-[3-methoxy-5-(4-morpholinyl)-2-pyrazinyl]benzenesulphonamide

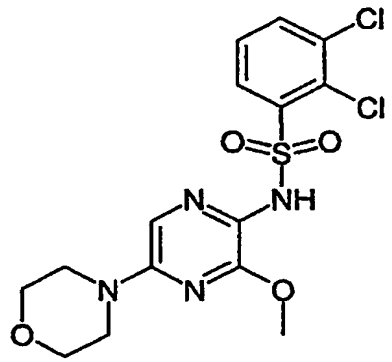
a) *N*-(5-Bromo-3-methoxy-2-pyrazinyl)-2,3-dichloro-*N*-[{2-(trimethylsilanyl)ethoxy}methyl]benzenesulphonamide



A mixture of *N*-(5-Bromo-3-methoxy-2-pyrazinyl)-2,3-dichlorobenzenesulphonamide (Example 8) (0.40g), diisopropylethylamine (0.26g) and [2-(chloromethoxy)ethyl]trimethylsilane (0.25g) in dichloromethane (50mL) was stirred at room temperature. After 2h, the solution was washed with water, dried ($MgSO_4$) and evaporated. Chromatography on silica gel eluting with ethyl acetate/isohexane mixtures gave the title compound as a white solid (0.40g).

^{1}H NMR ($CDCl_3$) δ 8.09 (1H, s), 7.96 (1H, dd), 7.68 (1H, dd), 7.29 (1H, t), 5.24 (2H, s), 3.92 (3H, s), 3.77-3.73 (2H, m), 0.86-0.82 (2H, m), 0.00 (9H, s)

b) 2,3-Dichloro-*N*-[3-methoxy-5-(4-morpholinyl)-2-pyrazinyl]benzenesulphonamide

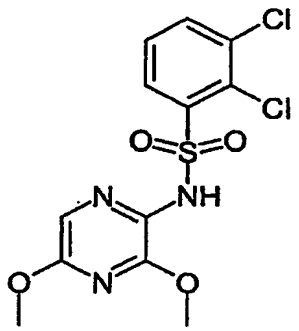


N-(5-Bromo-3-methoxy-2-pyrazinyl)-2,3-dichloro-*N*-[{2-(trimethylsilanyl)ethoxy}methyl]benzenesulphonamide (0.30g) and morpholine (0.45g) in acetonitrile (10mL) was heated at 50°C. After 16h, the solution was evaporated. Chromatography on silica gel eluting with ethyl acetate/isohexane mixtures gave the title compound with SEM group attached, as a white solid. The solid was dissolved in trifluoroacetic acid (5.0mL) and dichloromethane

(5.0mL). After 2h, the solution was evaporated. Chromatography on silica gel eluting with ethyl acetate/isohexane mixtures gave the title compound as a white solid (0.06g).
m/e 417 ($M-1^+$, 100%)
^{1}H NMR ($CDCl_3$) δ 8.17 (1H, d), 7.65 (1H, d), 7.41 (1H, s), 7.34 (1H, t), 7.16 (1H, s), 3.89 (3H, s), 3.80-3.75 (4H, m), 3.40-3.35 (4H, m)
MP 167-168°C

Example 56

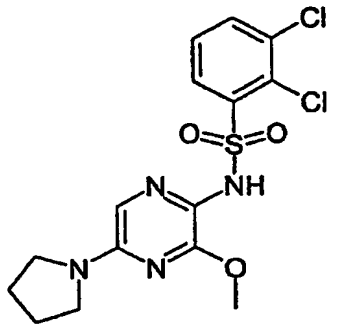
2,3-Dichloro-*N*-[3,5-dimethoxy-2-pyrazinyl]benzenesulphonamide



N-(5-Bromo-3-methoxy-2-pyrazinyl)-2,3-dichloro-*N*-[{2-(trimethylsilanyl)ethoxy}methyl]benzenesulphonamide (0.30g) in methanolic sodium methoxide (10mL of 0.5 molar solution) was strirred at room temperature. After 16h, the solution was evaporated to dryness and dichloromethane (10mL) and trifluoroacetic acid (10mL) added. After 2h, the mixture was evaporated to dryness, dichloromethane added and the inorganic salts removed by filtration. Chromatography on silica gel eluting with ethyl acetate/isohexane mixtures gave the title compound as a white solid (0.1g).
m/e 364 ($M+1^+$, 100%)
^{1}H NMR ($CDCl_3$) δ 8.21 (1H, d), 7.67 (1H, d), 7.50 (1H, s), 7.37 (1H, t), 7.26 (1H, s), 3.98 (3H, s), 3.87 (3H, s)
MP 138-139°C

Example 57

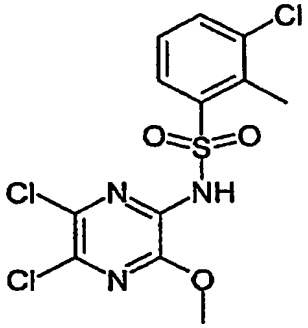
2,3-Dichloro-*N*-[3-methoxy-5-(1-pyrrolinyl)-2-pyrazinyl]benzenesulphonamide



Prepared by the method of Example 55 using pyrrolidine and *N*-(5-bromo-3-methoxy-2-pyrazinyl)-2,3-dichloro-*N*-[{2-(trimethylsilanyl)ethoxy}methyl]benzenesulphonamide.
m/e 403 ($M+1^+$, 100%)
^{1}H NMR ($CDCl_3$) δ 8.08 (1H, d), 7.64 (1H, d), 7.30 (1H, t), 7.21 (1H, s), 6.99 (1H, s), 3.81 (3H, s), 3.40-3.35 (4H, m), 2.00-1.95 (4H, m)
MP 179-180°C

Example 58

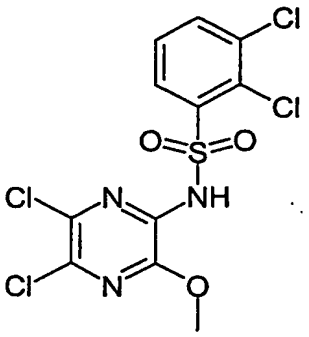
3-Chloro-*N*-(5,6-dichloro-3-methoxy-2-pyrazinyl)-2-methylbenzenesulphonamide



Prepared by the method of Example 1 using 5,6-dichloro-3-methoxy-2-pyrazinamine and 3-chloro-2-methylbenzenesulphonyl chloride.
m/e 381 ($M-1^+$, 100%)
^{1}H NMR ($CDCl_3$) δ 8.25 (1H, d), 7.65 (1H, br s), 7.62 (1H, d), 7.35 (1H, t), 4.04 (3H, s), 2.73 (3H, s)
MP 177-178°C

Example 59

2,3-Dichloro-*N*-(5,6-dichloro-3-methoxy-2-pyrazinyl)benzenesulphonamide



Prepared by the method of Example 1 using 5,6-dichloro-3-methoxy-2-pyrazinamine and 2,3-dichlorobenzenesulphonyl chloride

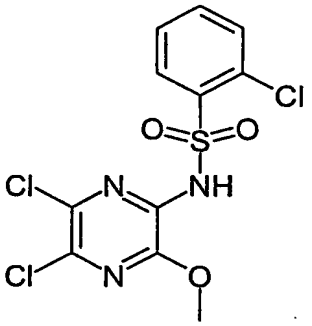
m/e 402 ($M-1^+$, 100%)

^{1}H NMR ($CDCl_3$) δ 8.31 (1H, d), 7.81 (1H, br s), 7.72 (1H, d), 7.45 (1H, t), 4.05 (3H, s)

MP 172-173°C

Example 60

2-Chloro-*N*-(5,6-dichloro-3-methoxy-2-pyrazinyl)benzenesulphonamide



Prepared by the method of Example 1 using 5,6-dichloro-3-methoxy-2-pyrazinamine and 2-chlorobenzenesulphonyl chloride.

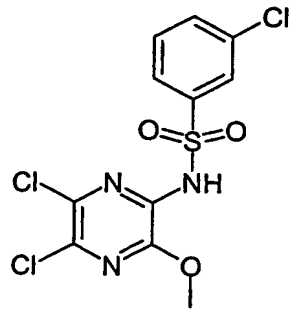
m/e 367 ($M-1^+$, 100%)

^{1}H NMR ($CDCl_3$) δ 8.39 (1H, d), 7.79 (1H, br s), 7.58-7.45 (3H, m), 4.04 (3H, s)

MP 217-218°C

Example 61

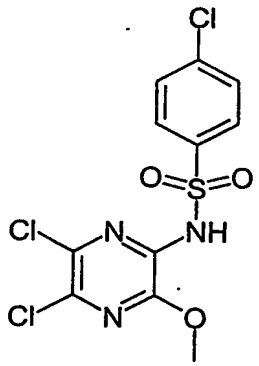
3-Chloro-*N*-(5,6-dichloro-3-methoxy-2-pyrazinyl)benzenesulphonamide



Prepared by the method of Example 1 using 5,6-dichloro-3-methoxy-2-pyrazinamine and 3-chlorobenzenesulphonyl chloride.
m/e 367 ($M-1^+$, 100%)
^{1}H NMR ($CDCl_3$) δ 8.19 (1H, s), 8.07 (1H, d), 7.61 (1H, d), 7.59 (1H, br s), 7.50 (1H, t), 4.02 (3H, s)
MP 171-172°C

Example 62

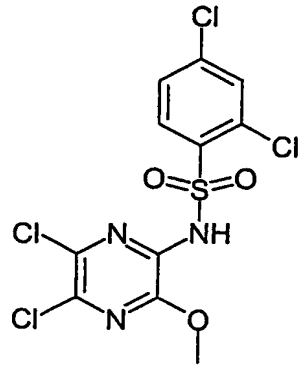
4-Chloro-*N*-(5,6-dichloro-3-methoxy-2-pyrazinyl)benzenesulphonamide



Prepared by the method of Example 1 using 5,6-dichloro-3-methoxy-2-pyrazinamine and 4-chlorobenzenesulphonyl chloride.
m/e 367 ($M-1^+$, 100%)
^{1}H NMR ($CDCl_3$) δ 8.11 (2H, d), 7.57 (1H, br s), 7.50 (2H, d), 4.02 (3H, s)
MP 186-187°C

Example 63

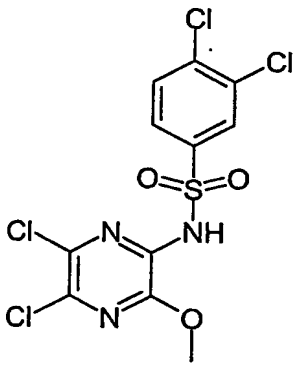
2,4-Dichloro-*N*-(5,6-dichloro-3-methoxy-2-pyrazinyl)benzenesulphonamide



Prepared by the method of Example 1 using 5,6-dichloro-3-methoxy-2-pyrazinamine and 2,4-dichlorobenzenesulphonyl chloride.
m/e 402 ($M-1^+$, 100%)
^{1}H NMR ($CDCl_3$) δ 8.30 (1H, d), 7.76 (1H, br s), 7.50 (1H, s), 7.48 (1H, d), 4.05 (3H, s)
MP 171-172°C

Example 64

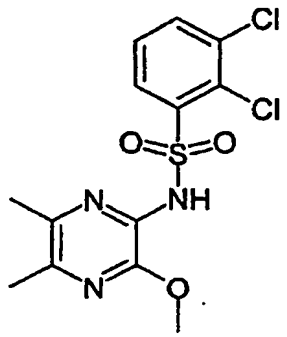
3,4-Dichloro-*N*-(5,6-dichloro-3-methoxy-2-pyrazinyl)benzenesulphonamide



Prepared by the method of Example 1 using 5,6-dichloro-3-methoxy-2-pyrazinamine and 3,4-dichlorobenzenesulphonyl chloride.
m/e 402 ($M-1^+$, 100%)
^{1}H NMR ($CDCl_3$) δ 8.30 (1H, s), 8.01 (1H, d), 7.63 (1H, d), 7.58 (1H, br s), 4.03 (3H, s)
MP 189-191°C

Example 65

2,3-Dichloro-*N*-(3-methoxy-5,6-dimethyl-2-pyrazinyl)benzenesulphonamide

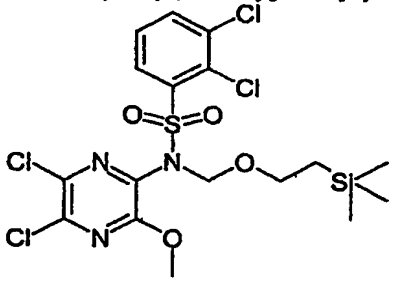


Prepared by the method of Example 1 using 3-methoxy-5,6-dimethyl-2-pyrazinamine and 2,3-dichlorobenzenesulphonyl chloride.
m/e 360 ($M-1^+$, 100%)
^{1}H NMR ($CDCl_3$) δ 8.32 (1H, d), 7.67 (1H, s), 7.65 (1H, d), 7.39 (1H, t), 3.95 (3H, s), 2.28 (3H, s), 2.14 (3H, s)
MP 165-166°C

Example 66

2,3-Dichloro-*N*-(6-chloro-3,5-dimethoxy-2-pyrazinyl)benzenesulphonamide

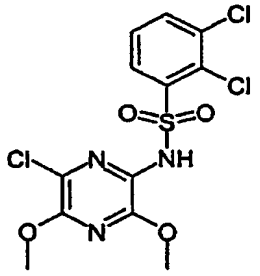
a) 2,3-Dichloro-*N*-(5,6-dichloro-3-methoxy-2-pyrazinyl)-*N*-{[2-(trimethylsilyl)ethoxy]methyl}benzenesulphonamide



To a stirred solution of 2,3-Dichloro-*N*-(5,6-dichloro-3-methoxypyrazin-2-yl)benzenesulphonamide (0.68g) in dichloromethane (20mL) was added triethylamine (0.491mL) followed by 2-(trimethylsilyl)ethoxymethyl chloride (0.328g) and the resulting mixture was stirred at room temperature for 1 h. The reaction mixture was poured into water (50mL) and extracted into ethyl acetate (3x20mL). The combined extracts were dried ($MgSO_4$), filtered and concentrated. Chromatography on silica gel eluting with ethyl acetate/isohexane mixtures gave the sub-title compound as a white solid (0.74g).

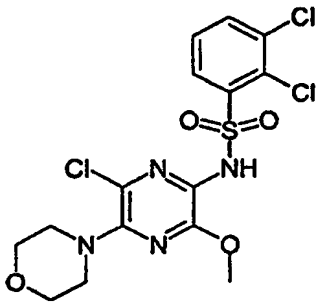
^{1}H NMR ($CDCl_3$) δ 8.02 (1H, dd), 7.70 (1H, dd), 7.34 (1H, t), 5.22 (2H, s), 3.96 (3H, s), 3.73 (2H, dd), 0.91-0.79 (2H, m), -0.03 (9H, s)

b) 2,3-Dichloro-*N*-(6-chloro-3,5-dimethoxy-2-pyrazinyl)benzenesulphonamide



2,3-Dichloro-*N*-(5,6-dichloro-3-methoxy-2-pyrazinyl)-*N*-{[2-(trimethylsilyl)ethoxy]methyl}benzenesulfonamide (0.10g) was dissolved in methanol (1.0mL) and a solution of sodium methoxide in methanol (0.1mL of a 25% solution in methanol) was added. The reaction was stirred at room temperature for 30 min and was concentrated. The residue was dissolved in trifluoroacetic acid (2.0mL) and was stirred at room temperature for 30 min. The reaction mixture was concentrated and chromatography on silica gel eluting with ethyl acetate/isohexane mixtures gave the title compound as a white solid (0.028g).
m/e 397 ($M\text{-}1^+$, 100%)
^{1}H NMR ($CDCl_3$) δ 8.26 (1H, d), 7.69 (1H, d), 7.41 (1H, t), 7.41 (1H, br s), 4.02 (3H, s), 3.91 (3H, s)
MP 163-165°C

Example 67
2,3-Dichloro-*N*-[6-chloro-3-methoxy-5-(4-morpholinyl)-2-pyrazinyl]benzenesulphonamide



2,3-Dichloro-N-(5,6-dichloro-3-methoxy-2-pyrazinyl)-*N*-{[2-(trimethylsilyl)ethoxy]methyl}benzenesulphonamide (Example 66 part a) (0.10 g) was dissolved in THF (1.0mL) and a solution of morpholine (0.05g) in THF (0.1mL) was added. The reaction was stirred at room temperature for 30 min and was concentrated. The residue was dissolved in trifluoroacetic acid (2.0mL) and dichloromethane (2.0mL) and was stirred at room temperature for 30 min. The reaction mixture was concentrated and chromatography on silica gel eluting with ethyl acetate/isohexane mixtures gave the title compound as a white solid (0.042g).

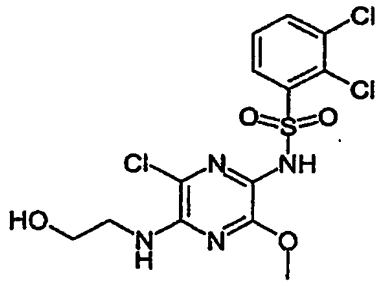
m/e 452 ($M\text{-}1^+$, 100%)

^{1}H NMR ($CDCl_3$) δ 8.28 (1H, dd), 7.69 (1H, dd), 7.49 (1H, br s), 7.43 (1H, t), 3.96 (3H, s), 3.79 (4H, dd), 3.28 (4H, dd)

MP 150-151°C

Example 68

2,3-Dichloro-*N*-[6-chloro-5-(2-hydroxyethylamino)-3-methoxy-2-pyrazinyl]benzenesulphonamide

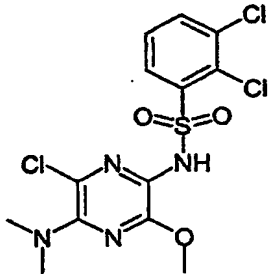


Prepared by the method of Example 67 using 2-aminoethanol and 2,3-dichloro-*N*-(5,6-dichloro-3-methoxy-2-pyrazinyl)-*N*-{[2-(trimethylsilyl)ethoxy]methyl}benzenesulfonamide. m/e 426 ($M\text{-}1^+$, 100%)

^{1}H NMR (D6-DMSO) δ 10.31 (1H, s), 7.91 (2H, dd), 7.52 (1H, t), 6.89 (1H, br s), 4.71 (1H, t), 3.63 (3H, s), 3.53 (2H, dd), 3.40 (2H, dd)

Example 69

2,3-Dichloro-*N*-[6-chloro-5-dimethylamino-3-methoxy-2-pyrazinyl]benzenesulphonamide



Prepared by the method of Example 67 using dimethylamine and 2,3-dichloro-*N*-(5,6-dichloro-3-methoxy-2-pyrazinyl)-*N*-{[2-(trimethylsilyl)ethoxy]methyl}benzenesulfonamide

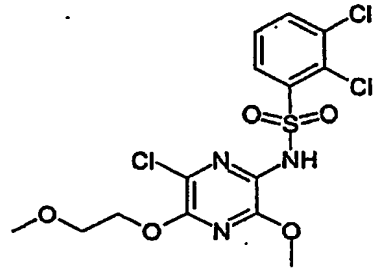
m/e 410 (M-1$^+$, 100%)

^{1}H NMR (D6-DMSO) δ 7.99-7.93 (2H, m), 7.56 (1H, t), 3.74 (3H, s), 2.99 (6H, s)

MP 145-146°C

Example 70

2,3-Dichloro-*N*-[6-chloro-3-methoxy-5-(2-methoxyethoxy)-2-pyrazinyl]benzenesulphonamide

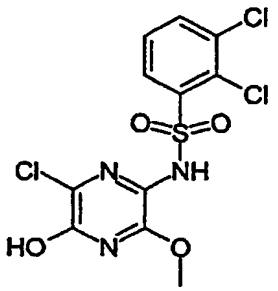


Sodium hydride (0.019g of 60% dispersion in oil) was added to a solution of 2,3-dichloro-*N*-(5,6-dichloro-3-methoxy-2-pyrazinyl)-*N*-{[2-(trimethylsilyl)ethoxy]methyl}benzenesulfonamide (0.25g) in 2-methoxyethanol (3.0mL) at room temperature. After 16h, the solvent was evaporated and trifluoroacetic acid (2.0mL) added. After 1h, the reaction mixture was concentrated and chromatography on

silica gel eluting with ethyl acetate/isohexane mixtures gave the title compound as a white solid (0.08g).
m/e 442 ($M+1^+$, 100%)
^{1}H NMR ($CDCl_3$) δ 8.24 (1H, dd), 7.70 (1H, dd), 7.41 (1H, t), 4.50-4.40 (2H, m), 3.96 (3H, s), 3.80-3.70 (2H, m), 3.42 (3H, s)
MP 193-194°C

Example 71

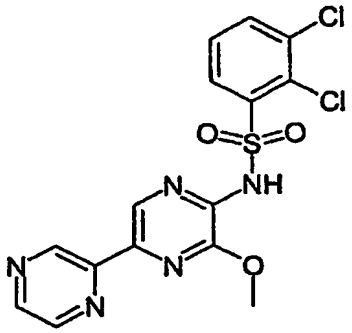
2,3-Dichloro-*N*-[6-chloro-5-hydroxy-3-methoxy-2-pyrazinyl]benzenesulphonamide



tetrabutylammonium hydroxide (0.28g of 40% aqueous solution) was added to a solution of 2,3-dichloro-*N*-(5,6-dichloro-3-methoxy-2-pyrazinyl)-*N*-{[2-(trimethylsilyl)ethoxy]methyl}benzenesulfonamide (0.25g) in 1,2-dimethoxyethane (3.0mL) at room temperature. After 16h, the solution was diluted with ethyl acetate (20mL). The organic solution was washed with aqueous citric acid (10mL) and brine, dried ($MgSO_4$) and evaporated. Chromatography on silica gel eluting with ethyl acetate/isohexane mixtures gave the title compound containing the SEM group, as a white solid (0.08g). The solid was dissolved in trifluroacetic acid (2.0mL) and dichloromethane (2.0mL) and stirred at room temperature for 1h. The reaction mixture was concentrated and chromatography on silica gel eluting with ethyl acetate/isohexane mixtures gave the title compound as a white solid (0.027g).
m/e 384 ($M+1^+$, 100%)
^{1}H NMR ($CDCl_3$) δ 12.56 (1H, s), 10.87 (1H, s), 7.96 (2H, t), 7.56 (1H, t), 3.74 (3H, s)

Example 72

2,3-Dichloro-*N*-[6-methoxy-5-([2,2']bipyrazinylyl)]benzenesulphonamide



N-(5-Bromo-3-methoxy-2-pyrazinyl)-2,3-dichloro-*N*-[{2-(trimethylsilanyl)ethoxy}methyl]benzenesulphonamide (Example 55 part a) (0.70g), tetrakis(triphenylphosphine)palladium(0) (0.1g) and 2-(tributylstannanyl)pyrazine (0.50g) in toluene (20mL) was heated under nitrogen at 100°C. After 16h, chromatography on silica gel eluting with ethyl acetate/isohexane mixtures gave the title compound protected with the SEM group as a white solid. The solid was dissolved in trifluoroacetic acid (2.0mL) and dichloromethane (2.0mL) and stirred at room temperature for 1h. The reaction mixture was concentrated, toluene added and evaporated. The title compound crystallised from acetonitrile to give a white solid (0.38g).

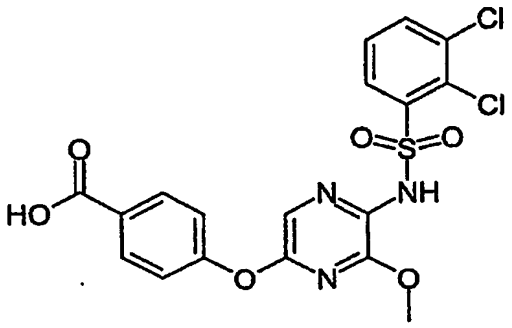
m/e 410 ($M\text{-}1^+$, 100%)

^{1}H NMR (D6 DMSO) δ 9.35 (1H, s), 8.69 (1H, d), 8.67 (1H, d), 8.40 (1H, br s), 8.14 (1H, d), 7.96 (1H, d), 7.61 (1H, t), 4.07 (3H, s)

MP 199-200°C

Example 73

4-[5-(2,3-Dichlorobenzenesulphonylamino)-6-methoxy-pyrazin-2-yloxy]benzoic acid



4-Hydroxybenzoic acid *tert* butyl ester (0.13g), *N*-(5-bromo-3-methoxy-2-pyrazinyl)-2,3-dichloro-*N*-[{2-(trimethylsilanyl)ethoxy}methyl]benzenesulphonamide (Example 55 part a) (0.35g) and caesium carbonate (0.42g) in acetonitrile (10mL) was heated at 50°C. After

12h, the mixture was diluted with ethyl acetate, washed with water, dried ($MgSO_4$) and evaporated. Chromatography on silica gel eluting with ethyl acetate/isohexane mixtures gave the title compound protected with the SEM group and *tert* butyl group as an oil. The oil was dissolved in trifluoroacetic acid (2.0mL) and stirred at room temperature for 3h. The reaction mixture was concentrated, toluene added and evaporated to give the title compound as a white solid (0.19g).

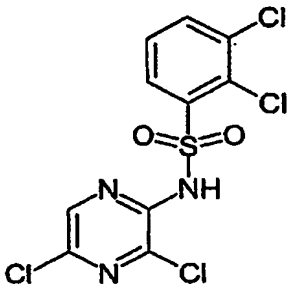
m/e 468 ($M\text{-}1^+$, 100%)

^{1}H NMR ($CDCl_3$) δ 8.28 (1H, d), 8.11 (2H, d), 7.80 (1H, br s), 7.71 (1H, d), 7.45 (2H, m), 7.12 (2H, d), 3.89 (3H, s)

MP 186-187°C

Example 74

2,3-Dichloro-*N*-(3,5-dichloro-2-pyrazinyl)benzenesulphonamide



Prepared by the method of Example 1 using 3,5-dichloro-2-pyrazinamine and 2,3-dichloro benzenesulphonyl chloride.

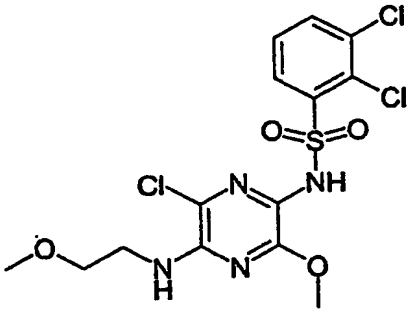
m/e 372 ($M\text{-}1^+$, 100%)

^{1}H NMR (D6 DMSO) δ 8.29 (1H, s), 8.06 (1H, dd), 7.94 (1H, dd), 7.57 (1H, t)

MP 181-182°C

Example 75

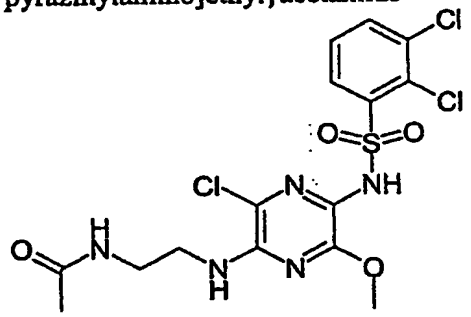
2,3-Dichloro-*N*-[6-chloro-3-methoxy-5-({2-methoxyethyl}amino)-2-pyrazinyl]benzenesulphonamide



Prepared by the method of Example 67 using 2-methoxyethylamine and 2,3-dichloro-*N*-(5,6-dichloro-3-methoxy-2-pyrazinyl)-*N*-{[2-(trimethylsilyl)ethoxy]methyl}benzenesulphonamide. m/e 439 ($M+1^+$, 100%)
^{1}H NMR (D6-DMSO) δ 10.33 (1H, s), 7.92 (2H, dd), 7.52 (1H, t), 7.00 (1H, s), 3.64 (3H, s), 3.47 (4H, s), 3.24 (2H, dd)
MP 177-178°C

Example 76

N-{2-[3-Chloro-5-(2,3-dichlorobenzenesulphonylamino)-6-methoxy-2-pyrazinylamino]ethyl}acetamide

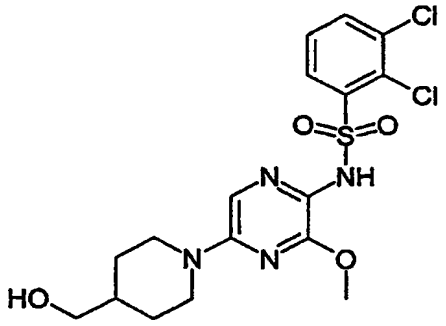


2,3-Dichloro-N-(5,6-dichloro-3-methoxy-2-pyrazinyl)-*N*-{[2-(trimethylsilyl)ethoxy]methyl}benzenesulphonamide (Example 66 part a) (0.26g) was dissolved in acetonitrile (1.0mL) and *N*-acetylethylenediamine (0.055mL) and triethylamine (0.19mL) added. After 48h, the reaction mixture was concentrated and chromatography on silica gel eluting with ethyl acetate gave the title compound protected with the SEM group, as an oil (0.13g). The oil was dissolved in dichloromethane (2.0mL) and boron trifluoride etherate (0.14ml) added. After 2h, ethyl acetate (20mL) was added and the mixture washed with 5% aqueous citric acid (5mL), dried ($MgSO_4$) and evaporated. Chromatography on silica gel eluting with ethyl acetate gave the title compound as a solid (0.031g).

m/e 470 ($M+1^+$, 100%)
^{1}H NMR (D6-DMSO) δ 10.32 (1H, s), 7.93-7.88 (2H, m), 7.52 (1H, t), 7.10 (1H, s), 3.65 (3H, s), 3.40-3.10 (4H, m), 1.75 (3H, s)
MP 150-152°C

Example 77

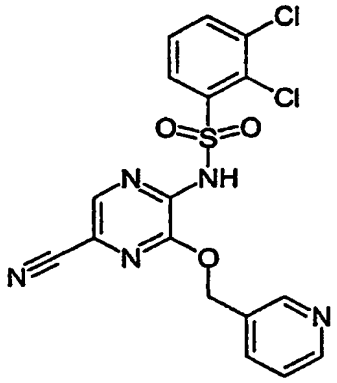
2,3-Dichloro-*N*-[5-(4-hydroxymethyl-1-piperidinyl)-3-methoxy-2-pyrazinyl]benzenesulphonamide



Prepared by the method of Example 55 using 4-(hydroxymethyl)piperidine and *N*-(5-bromo-3-methoxy-2-pyrazinyl)-2,3-dichloro-*N*-[{2-(trimethylsilanyl)ethoxy}methyl]benzenesulphonamide.
m/e 447 ($M+1^+$, 100%)
^{1}H NMR ($CDCl_3$) δ 8.14 (1H, dd), 7.65 (1H, dd), 7.33 (1H, t), 7.20 (1H, s), 4.20-4.10 (2H, m), 3.86 (3H, s), 3.60-3.50 (2H, m), 2.90-2.70 (2H, m), 1.90-1.70 (3H ,m), 1.40-1.20 (3H, m)

Example 78

2,3-Dichloro-*N*-[5-cyano-3-(3-pyridinylmethoxy)-2-pyrazinyl]benzenesulphonamide



N-[5-Bromo-3-(3-pyridinylmethoxy)-2-pyrazinyl]-2,3-dichlorobenzenesulphonamide (Example 34) (0.15g), tetrakis(triphenylphosphine)palladium(0) (0.04g) and zinc cyanide (0.03g) in *N,N*-dimethylformamide (5.0mL) was heated at 70°C. After 5h, the mixture was diluted with ethyl acetate (30mL) and washed with 5% aqueous citric acid (5mL), dried ($MgSO_4$) and evaporated. Chromatography on silica gel eluting with ethyl acetate/isohexane mixtures containing 1% acetic acid gave the title compound as a white solid (0.058g).

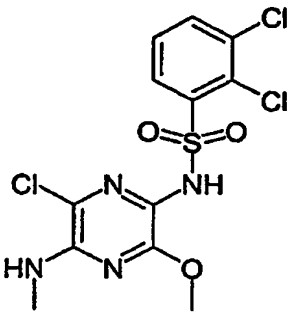
m/e 436 ($M+1^+$, 100%)

^1H NMR (D6 DMSO) δ 8.70-7.65 (2H, m), 8.29 (1H, dd), 7.99 (1H, s), 7.78 (1H, d), 7.73 (1H, dd), 7.46 (1H, t), 7.40-7.35 (1H, m), 5.45 (2H, s)

MP 222-224°C

Example 79

2,3-Dichloro-*N*-(6-chloro-3-methoxy-5-methylamino-2-pyrazinyl)benzenesulphonamide

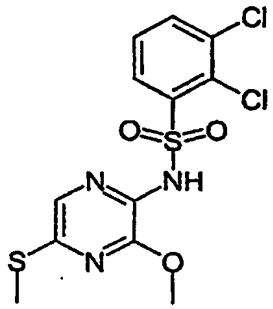


3-Dichloro-N-(5,6-dichloro-3-methoxy-2-pyrazinyl)-*N*-{[2-(trimethylsilyl)ethoxy]methyl}benzenesulphonamide (Example 66 part a) (0.25 g) was dissolved in methanol (1.0mL) and methylamine (2.0mL of 40% aqueous solution) was added. After 16h, the solution was partitioned between water and ethyl acetate. The

organic layer was dried ($MgSO_4$) and evaporated. The residue was dissolved in dichloromethane (2.0 mL) and boron trifluoride etherate (0.25mL) added. After 1h, ethyl acetate (20mL) was added and the solution washed with 5% aqueous citric acid (5mL), dried ($MgSO_4$) and evaporated. Chromatography on silica gel eluting with ethyl acetate/isohexane mixtures gave the title compound as a white solid (0.05g).
m/e 395 ($M+1^+$, 100%)
^{1}H NMR (D6-DMSO) δ 10.27 (1H, s), 7.95-7.87 (2H, m), 7.51 (1H, dd), 7.10-7.00 (1H, m), 3.64 (3H, s), 2.84 (3H, s)
MP 185-186°C

Example 80

2,3-Dichloro-*N*-(3-methoxy-5-methylsulphanyl-2-pyrazinyl)benzenesulphonamide (AR-C

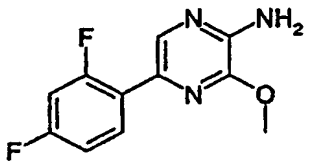


N-(5-Bromo-3-methoxy-2-pyrazinyl)-2,3-dichloro-*N*-[{2-(trimethylsilanyl)ethoxy}methyl]benzenesulphonamide (0.30g) and sodium thiomethoxide (0.05g) in acetonitrile (10mL) was stirred at room temperature. After 2h, the solution was evaporated. Chromatography on silica gel eluting with ethyl acetate/isohexane mixtures gave the title compound with SEM group attached. The compound was dissolved in trifluoroacetic acid (5mL). After 2h, toluene (20mL) was added and the solution evaporated, . Chromatography on silica gel eluting with ethyl acetate/isohexane mixtures gave the title compound as a white solid (0.16g).
m/e 380 ($M+1^+$, 100%)
^{1}H NMR ($CDCl_3$) δ 8.25 (1H, d), 7.70 (1H, s), 7.68 (1H, d), 7.52 (1H, s), 7.39 (1H, t), 4.03 (3H, s), 2.48 (3H, s)
MP 141-142°C

Example 81

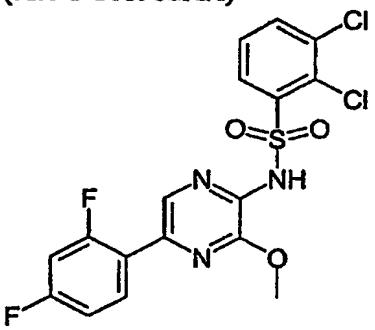
2,3-Dichloro-*N*-[5-(2,4-difluorophenyl)-3-methoxy-2-pyrazinyl]benzenesulphonamide

a) 5-(2,4-difluorophenyl)-3-methoxy-2-pyrazinamine



5-Bromo-3-methoxy-2-pyrazinamine (0.3g), cesium fluoride (0.8g), 2,4-difluorobenezeneboronic acid (0.4g) and [1,1'-bis(diphenylphosphino)ferrocene]palladium (II) chloride (0.04g) in methanol (20mL) was heated at 70°C . After 6h, the solvent was evaporated and the residue purified by chromatography on silica eluting with ethyl acetate/isohexane mixtures to give the sub-title compound (0.2g).

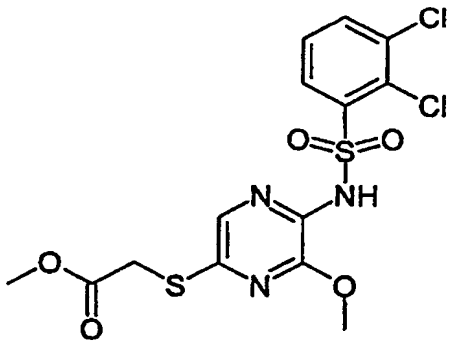
b) 2,3-Dichloro-*N*-[5-(2,4-difluorophenyl)-3-methoxy-2-pyrazinyl]benzenesulphonamide (AR-C 161982XX)



Prepared by the method of Example 1 using 5-(2,4-difluorophenyl)-3-methoxy-2-pyrazinamine and 2,3-dichlorobenzenesulphonyl chloride.
m/e 444 ($M-1^+$, 100%)
^{1}H NMR (D6-DMSO) δ 8.15 (1H, d), 8.05-7.95 (2H, m), 7.93 (1H, d), 7.60 (1H, t), 7.45-7.35 (1H, m), 7.30-7.20 (1H, m), 4.03 (3H, s)
MP 169-170°C

Example 82

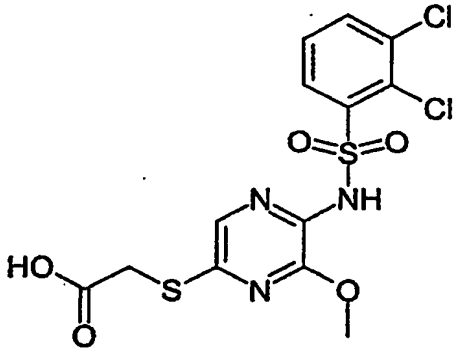
[5-(2,3-Dichlorobenzenesulphonylamino)-6-methoxy-2-pyrazinylsulphanyl]acetic acid methyl ester



N-(5-Bromo-3-methoxy-2-pyrazinyl)-2,3-dichloro-*N*-[{2-(trimethylsilanyl)ethoxy}methyl]benzenesulphonamide (0.40g), mercaptoacetic acid methyl ester (0.1g) and caesium carbonate (0.6g) in acetonitrile (10mL) was stirred at room temperature. After 16h, the solution was diluted with dichloromethane, filtered and evaporated. Chromatography on silica gel eluting with ethyl acetate/isohexane mixtures gave the title compound with SEM group attached. The compound was dissolved in trifluoroacetic acid (5mL). After 2h, toluene (20mL) was added and the solution evaporated, . Chromatography on silica gel eluting with ethyl acetate/isohexane mixtures gave the title compound as a white solid (0.15g).
m/e 438 ($M+1^+$, 100%)
^{1}H NMR ($CDCl_3$) δ8.26 (1H, dd), 7.73 (1H, s), 7.68 (1H, dd), 7.59 (1H, s), 7.41 (1H, t), 3.99 (3H, s), 3.80 (2H, s), 3.71 (3H, s)
MP 152-153°C

Example 83

[5-(2,3-Dichlorobenzenesulphonylamino)-6-methoxy-2-pyrazinylsulphanyl]acetic acid



[5-(2,3-Dichlorobenzenesulphonylamino)-6-methoxy-2-pyrazinylsulphanyl]acetic acid methyl ester (Example 82) (0.1g) and lithium hydroxide (0.04g) in methanol (5mL) and water (1mL) was stirred at room temperature. After 2h, the mixture was evaporated and saturated aqueous citric acid (5mL) added. The white solid was collected, washed with water and dried. Yield 0.07g.

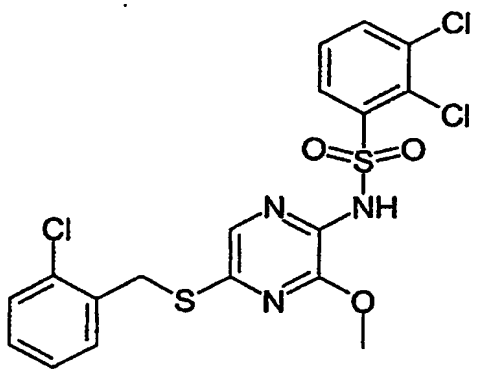
m/e 424 ($M+1^+$, 100%)

^{1}H NMR ($CDCl_3$) δ 8.27 (1H, dd), 7.90 (1H, br s), 7.70 (1H, dd), 7.61 (1H, s), 7.40 (1H, t), 3.98 (3H, s), 3.80 (2H, s)

MP 138-140°C

Example 84

2,3-Dichloro-*N*-[5-(2-chlorobenzylsulphanyl)-3-methoxy-2-pyrazinyl]benzenesulphonamide



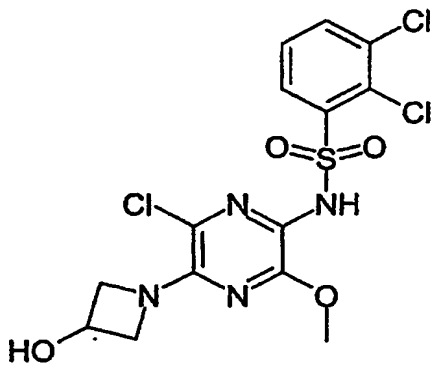
Prepared by the method of Example 82 using 2-chlorobenzylmercaptan and *N*-(5-bromo-3-methoxy-2-pyrazinyl)-2,3-dichloro-*N*-[{2-(trimethylsilanyl)ethoxy}methyl]benzenesulphonamide.

m/e 492 ($M+1^+$, 100%)

^{1}H NMR ($CDCl_3$) δ 8.26 (1H, dd), 7.73 (1H, s), 7.69 (1H, dd), 7.53 (1H, s), 7.40-7.30 (3H, m), 7.20-7.10 (2H, m), 4.39 (2H, s), 4.02 (3H, s)
MP 119-120°C

Example 85

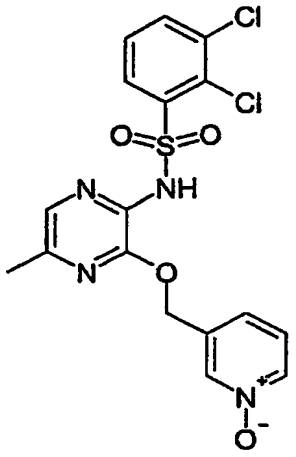
2,3-Dichloro-*N*-[6-chloro-5-(3-hydroxy-1-azetidinyl)-3-methoxy-2-pyrazinyl]benzenesulphonamide



2,3-Dichloro-N-(5,6-dichloro-3-methoxy-2-pyrazinyl)-*N*-{[2-(trimethylsilyl)ethoxy]methyl}benzenesulphonamide (Example 66 part a) (0.20 g), azetidin-3-ol hydrochloride (0.082g) and triethylamine (0.25mL) in acetonitrile (3mL) and water (0.5mL) was stirred at room temperature. After 2h, the mixture was evaporated and triturated with diethyl ether. The ethereal solution was evaporated and the residue dissolved in a 1molar solution of tetrabutylammonium fluoride in THF (6mL). After 16h, the reaction mixture was concentrated and chromatography on silica gel eluting with ethyl acetate/isohexane mixtures gave the title compound as a white solid (0.024g).
m/e 442 ($M+1^+$, 100%)
^{1}H NMR (D6-DMSO) δ 10.58 (1H, s), 7.92 (2H, d), 7.54 (1H, t), 5.66 (1H, s), 4.49 (1H, s), 4.36 (2H, t), 3.88 (2H, m), 3.67 (3H, s)
MP 93-95°C

Example 86

2,3-Dichloro-*N*-[5-methyl-3-(1-oxy-3-pyrazinylmethoxy)-2-pyrazinyl]benzenesulphonamide



2,3-Dichloro-*N*-[5-methyl-3-(3-pyridinylmethoxy)-2-pyrazinyl)benzenesulphonamide (Example 24) (0.2g) and 3-chloroperbenzoic acid (0.35g) in dichloromethane (4mL) was stirred at room temperature. After 0.5h, chromatography on silica gel eluting with 5% methanol in ethyl acetate containing 1% acetic acid gave the title compound as a white solid (0.16g).

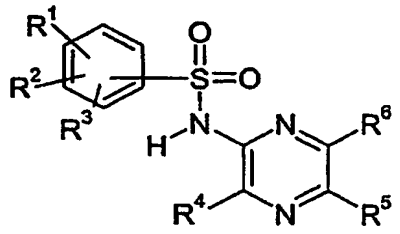
m/e 441 ($M+1^+$, 100%)

^{1}H NMR (D6-DMSO) δ 11.56 (1H, br s), 8.60 (1H, br s), 8.18 (1H, dt), 8.06 (1H, dd), 7.90 (1H, dd), 7.61 (1H, br s), 7.56 (1H, t), 7.50-7.40 (2H, m), 5.36 (2H, s), 2.28 (3H, s)

MP 223-228°C

CLAIMS

1. Aa compound of formula (I) and pharmaceutically acceptable salts, solvates or N-oxides thereof:



(I)

in which
R^1, R^2 and R^3 are independently hydrogen, halogen, cyano, CF_3, OCF_3, C_{1-6} alkenyl or C_{1-6} alkyl;
R^4 is halogen, C_{1-6} alkoxy or OR^9;
R^5 and R^6 are independently hydrogen, halogen, C_{1-6} alkoxy, C_{1-6} alkylthio, cyano, R^9, OR^9, NR^9R^{10}, SR^9, $S(CH2)_nCO_2H$, $S(CH2)_nCO_2R^{12}$, $S(CH2)_nCONR^{12}R^{13}$, $S(CH2)_nR^{11}$ or a 5- to 7-membered heteroaromatic or saturated ring containing 1 to 3 heteroatoms selected from nitrogen, oxygen and sulphur;
n is 1, 2 or 3;
R^9 and R^{10} are independently hydrogen, C_{1-6} alkyl optionally substituted by hydroxy, C_{1-6} alkoxy or $NHCOC_{1-6}$ alkyl, or R^9 and R^{10} are optionally substituted aryl, C_{1-6} alkyl-aryl or C_{1-6} alkyl-R^{11} or R^9 and R^{10} together with the nitrogen atom to which they are attached form a 4- to 8-membered saturated ring containing 1 to 3 heteroatoms selected from nitrogen, oxygen and sulphur and optionally substituted by C_{1-6} alkyl or C_{1-6} alkyl-OH or OH; and
R^{11} is a 5- to 7-membered heteraromatic ring containing 1 to 3 heteroatoms selected from nitrogen, oxygen and sulphur and optionally substituted by C_{1-6} alkyl;
R^{12} and R^{13} are independently hydrogen or C_{1-6} alkyl.

2. A compound according to claim 1 in which one of R^1, R^2 and R^3 is methyl, ethenyl, cyano, chloro, fluoro, iodo or two are chloro or all three are fluoro.

3. A compound according to claim 1 or 2 in which R^4 is halogen, C_{1-6} alkoxy, C_{1-6} alkyl or OR^9 where R^9 is CH_2R^{11} where R^{11} is a 5- or 6-membered heteroaromatic ring containing 1 or 2 heteroatoms .

4. A compound according to any one of claims 1 to 3 in which R^5 is hydrogen, methyl, bromo, chloro, methoxy, morpholinyl, pyrrolinyl, dimethylamino, hydroxy, 2-methoxyethoxy, pyrazinyl, O-Ph-CO_2H, 2-hydroxyethylamino, 2-methoxyethylamino, $NHCH_2CH_2NHCOMe$, cyano, 4-hydroxymethyl-1-piperidinyl, SMe, NHMe, or 2,4-difluorophenyl..

5. A compound according to any one of claims 1 to 3 in which R^6 is hydrogen or chloro

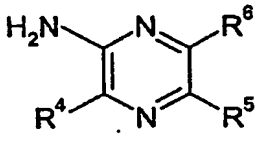
6. A compound according to claim 1 which is:
2,3-Dichloro-N-(3-methoxy-5-methyl-2-pyrazinyl)-benzenesulphonamide
N-(6-Chloro-3-methoxy-2-pyrazinyl)-2,3,4-tifluorobenzenesulphonamide
3-Chloro-N-(6-Chloro-3-methoxy-2-pyrazinyl)-2-methylbenzenesulphonamide
2,3-Dichloro-N-(6-Chloro-3-methoxy-2-pyrazinyl)benzenesulphonamide
2,3-Dichloro-N-(5-chloro-3-methoxy-2-pyrazinyl)benzenesulphonamide
N-(5-Bromo-3-methoxy-2-pyrazinyl)-2,5-dichlorobenzenesulphonamide
N-(5-Bromo-3-methoxy-2-pyrazinyl)-3,5-dichlorobenzenesulphonamide
N-(5-Bromo-3-methoxy-2-pyrazinyl)-2,3-dichlorobenzenesulphonamide
N-(5-Bromo-3-methoxy-2-pyrazinyl)-2,4-dichlorobenzenesulphonamide
N-(5-Bromo-3-methoxy-2-pyrazinyl)-3,4-dichlorobenzenesulphonamide
N-(5-Bromo-3-methoxy-2-pyrazinyl)-4-chlorobenzenesulphonamide
N-(5-Bromo-3-methoxy-2-pyrazinyl)-3-chlorobenzenesulphonamide
pyrazinamine
N-(5-Bromo-3-methoxy-2-pyrazinyl)-2-ethenylbenzenesulphonamide
N-(5-Bromo-3-methoxy-2-pyrazinyl)-2-fluorobenzenesulphonamide
N-(3-Methoxy-5-methyl-2-pyrazinyl)benzenesulphonamide
N-(3-Methoxy-5-methyl-2-pyrazinyl)-2-iodobenzenesulphonamide.
N-(3-Methoxy-5-methyl-2-pyrazinyl)-3-fluorobenzenesulphonamide
2-[[(3-Methoxy-5-methyl-2-pyrazinyl)amino]sulphonyl]benzonitrile
N-(5-Bromo-3-methoxy-2-pyrazinyl)benzenesulphonamide
N-(5-Bromo-3-methoxy-2-pyrazinyl)2-iodobenzenesulphonamide,
2,3-Dichloro-*N*-[3-(2-furanylmethoxy)-5-methyl-2-pyrazinyl)benzenesulphonamide

2,3-Dichloro-*N*-[5-methyl-3-(5-methyl-3-isoxazolylmethoxy)-2-pyrazinyl)benzenesulphonamide
2,3-Dichloro-*N*-[5-methyl-3-(2-pyridinylmethoxy)-2-pyrazinyl)benzenesulphonamide
2,3-Dichloro-*N*-[5-methyl-3-(6-methyl-2-pyridinylmethoxy)-2-pyrazinyl)benzenesulphonamide
2,3-Dichloro-*N*-[5-methyl-3-(3-pyridinylmethoxy)-2-pyrazinyl)benzenesulphonamide
2,3-Dichloro-*N*-[5-methyl-3-(4-pyridinylmethoxy)-2-pyrazinyl)benzenesulphonamide
2,3-Dichloro-*N*-[5-methyl-3-(3-methyl-2-pyridinylmethoxy)-2-pyrazinyl)benzenesulphonamide
2,3-Dichloro-*N*-[5-methyl-3-(3-pyridazinylmethoxy)-2-pyrazinyl)benzenesulphonamide
2,3-Dichloro-*N*-[3-(2-pyridinylmethoxy)-2-pyrazinyl)benzenesulphonamide
2,3-Dichloro-*N*-[3-(3-pyridinylmethoxy)-2-pyrazinyl)benzenesulphonamide
2,3-Dichloro-*N*-[3-methoxy-2-pyrazinyl)benzenesulphonamide
N-[5-Bromo-3-(2-pyrazinylmethoxy)-2-pyrazinyl]-2,3-dichlorobenzenesulphonamide
N-[5-Bromo-3-(1-methyl-6-oxo-1,6-dihydro-3-pyridinylmethoxy)-2-pyrazinyl]-2,3-dichlorobenzenesulphonamide
N-[5-Bromo-3-(3-pyridazinyllmethoxy)-2-pyrazinyl]-2,3-dichlorobenzenesulphonamide
N-[5-Bromo-3-(3-pyridinylmethoxy)-2-pyrazinyl]-2,3-dichlorobenzenesulphonamide
N-[5-Bromo-3-(5-pyrimidinylmethoxy)-2-pyrazinyl]-2,3-dichlorobenzenesulphonamide
N-[5-Chloro-3-(3-pyridinylmethoxy)-2-pyrazinyl]-2,3-dichlorobenzenesulphonamide
N-[5-Chloro-3-(5-pyrimidinylmethoxy)-2-pyrazinyl]-2,3-dichlorobenzenesulphonamide
2-Chloro-*N*-(6-chloro-3-methoxy-2-pyrazinyl)benezenesulphonamide
3-Chloro-*N*-(6-chloro-3-methoxy-2-pyrazinyl)benezenesulphonamide
4-Chloro-*N*-(6-chloro-3-methoxy-2-pyrazinyl)benezenesulphonamide
N-(6-Chloro-3-methoxy-2-pyrazinyl)-2,4-dichlorobenezenesulphonamide
3-Chloro-N-(3-methoxy-5-methyl-2-pyrazinyl)-2-methylbenezenesulphonamide
2-Chloro-*N*-(3-methoxy-5-methyl-2-pyrazinyl)benezenesulphonamide
3-Chloro-*N*-(3-methoxy-5-methyl-2-pyrazinyl)benezenesulphonamide
4-Chloro-*N*-(3-methoxy-5-methyl-2-pyrazinyl)benezenesulphonamide
2,4-Dichloro-*N*-(3-methoxy-5-methyl-2-pyrazinyl)benezenesulphonamide
3,4-Dichloro-*N*-(3-methoxy-5-methyl-2-pyrazinyl)benezenesulphonamide
N-(5-Bromo-3-methoxy-2-pyrazinyl)-2-trifluoromethoxybenezenesulphonamide
3-Chloro-*N*-(5-chloro-3-methoxy-2-pyrazinyl)-2-methylbenzenesulphonamide
2-Chloro-*N*-(5-chloro-3-methoxy-2-pyrazinyl)benzenesulphonamide
3-Chloro-*N*-(5-chloro-3-methoxy-2-pyrazinyl)benzenesulphonamide
4-Chloro-*N*-(5-chloro-3-methoxy-2-pyrazinyl)benzenesulphonamide

N-(5-Chloro-3-methoxy-2-pyrazinyl)-2,4-dichlorobenzenesulphonamide
2,3-Dichloro-*N*-[3-methoxy-5-(4-morpholinyl)-2-pyrazinyl]benzenesulphonamide
2,3-Dichloro-*N*-[3,5-dimethoxy-2-pyrazinyl]benzenesulphonamide
2,3-Dichloro-*N*-[3-methoxy-5-(1-pyrrolinyl)-2-pyrazinyl]benzenesulphonamide
3-Chloro-*N*-(5,6-dichloro-3-methoxy-2-pyrazinyl)-2-methylbenzenesulphonamide
2,3-Dichloro-*N*-(5,6-dichloro-3-methoxy-2-pyrazinyl)benzenesulphonamide
2-Chloro-*N*-(5,6-dichloro-3-methoxy-2-pyrazinyl)benzenesulphonamide
3-Chloro-*N*-(5,6-dichloro-3-methoxy-2-pyrazinyl)benzenesulphonamide
4-Chloro-*N*-(5,6-dichloro-3-methoxy-2-pyrazinyl)benzenesulphonamide
2,4-Dichloro-*N*-(5,6-dichloro-3-methoxy-2-pyrazinyl)benzenesulphonamide
3,4-Dichloro-*N*-(5,6-dichloro-3-methoxy-2-pyrazinyl)benzenesulphonamide
2,3-Dichloro-*N*-(3-methoxy-5,6-dimethyl-2-pyrazinyl)benzenesulphonamide
2,3-Dichloro-*N*-(6-chloro-3,5-dimethoxy-2-pyrazinyl)benzenesulphonamide
2,3-Dichloro-*N*-[6-chloro-3-methoxy-5-(4-morpholinyl)-2-pyrazinyl]benzenesulphonamide
2,3-Dichloro-*N*-[6-chloro-5-(2-hydroxyethylamino)-3-methoxy-2-pyrazinyl]benzenesulphonamide
2,3-Dichloro-*N*-[6-chloro-5-dimethylamino-3-methoxy-2-pyrazinyl]benzenesulphonamide
2,3-Dichloro-*N*-[6-chloro-3-methoxy-5-(2-methoxyethoxy)-2-pyrazinyl]benzenesulphonamide
2,3-Dichloro-*N*-[6-chloro-5-hydroxy-3-methoxy-2-pyrazinyl]benzenesulphonamide
2,3-Dichloro-*N*-[6-methoxy-5-([2,2']bipyrazinylyl)]benzenesulphonamide
4-[5-(2,3-Dichlorobenzenesulphonylamino)-6-methoxy-pyrazin-2-yloxy]benzoic acid
2,3-Dichloro-*N*-(3,5-dichloro-2-pyrazinyl)benzenesulphonamide
2,3-Dichloro-*N*-[6-chloro-3-methoxy-5-({2-methoxyethyl}amino)-2-pyrazinyl]benzenesulphonamide
N-{2-[3-Chloro-5-(2,3-dichlorobenzenesulphonylamino)-6-methoxy-2-pyrazinylamino]ethyl}acetamide
2,3-Dichloro-*N*-[5-(4-hydroxymethyl-1-piperidinyl)-3-methoxy-2-pyrazinyl]benzenesulphonamide
2,3-Dichloro-*N*-[5-cyano-3-(3-pyridinylmethoxy)-2-pyrazinyl]benzenesulphonamide
2,3-Dichloro-*N*-(6-chloro-3-methoxy-5-methylamino-2-pyrazinyl)benzenesulphonamide
2,3-Dichloro-*N*-(3-methoxy-5-methylsulphanyl-2-pyrazinyl)benzenesulphonamide
2,3-Dichloro-*N*-[5-(2,4-difluorophenyl)-3-methoxy-2-pyrazinyl]benzenesulphonamide
[5-(2,3-Dichlorobenzenesulphonylamino)-6-methoxy-2-pyrazinylsulphanyl]acetic acid methyl ester

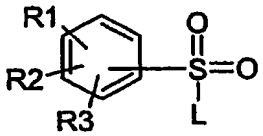
[5-(2,3-Dichlorobenzenesulphonylamino)-6-methoxy-2-pyrazinylsulphanyl]acetic acid
2,3-Dichloro-*N*-[5-(2-chlorobenzylsulphanyl)-3-methoxy-2-pyrazinyl]benzenesulphonamide
2,3-Dichloro-*N*-[6-chloro-5-(3-hydroxy-1-azetidinyl)-3-methoxy-2-pyrazinyl]benzenesulphonamide
2,3-Dichloro-*N*-[5-methyl-3-(1-oxy-3-pyrazinylmethoxy)-2-pyrazinyl]benzenesulphonamide
and pharmaceutically acceptable salts and solvates thereof.

7. A process for the preparation of a compound of formula (I) which comprises reaction of a compound of formula (II):



(II)

where R^4, R^5 and R^6 are as defined in formula (I) or are protected derivatives thereof with a compound of formula (III):



(III)

where R^1, R^2 and R^3 are as defined in formula (I) or are protected derivatives thereof and L is a leaving group,
and optionally thereafter

- removing any protecting groups,
- forming a pharmaceutically acceptable salt.

8. A pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in claim 1 in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

9. A process for the preparation of a pharmaceutical composition as claimed in claim 2 which comprises mixing a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in claim 1 with a pharmaceutically acceptable adjuvant, diluent or carrier.

10. Use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in claim 1 in the manufacture of a medicament for use in therapy.

11. A method of treating a chemokine mediated disease wherein the chemokine binds to one or more chemokine receptors, which comprises administering to a patient a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in claim 1.

12. A method according to claim 11 in which the chemokine receptor belongs to the CCR chemokine receptor subfamily.

13. A method according to claim 11 or 12 in which the chemokine receptor is the CCR4 receptor.

14 A method of treating an inflammatory disease in a patient suffering from, or at risk of, said disease, which comprises administering to the patient a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in claim 1.

15. A method according to claim 14, wherein the disease is asthma.

ABSTRACT

The invention provides phenylsulphonamides for use in therapy.